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THE HARVEY SOCIETY

THE

HARVEY LECTURES

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THE HARVEY SOCIETY

OF NEW YORK

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"The Harvey Society deserves the thanks of the profession at large for having organized such a series and for having made it possible for all medical readers to share the profits of the undertaking."

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THE HARVEY LECTURES

DELIVERED UNDER THE AUSPICES OF

THE HARVEY SOCIETY OF NEW YORK

1919-1920

BY

LIEUT.-COLONEL GEORGES DREYER
DR. H. H. DALE
DR. E. C. KENDALL
DR. HOMER F. SWIFT
DR. CARL VOEGTLIN
DR. OTTO FOLIN
DR. W. MCKIM MARRIOTT

SERIES XV

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PREFACE

The Fifteenth Series of Harvey Society Lectures is the first complete course given following the close of the World War. It is but natural, therefore, that it should represent a transition to the normal condition in medical investigation that existed before the outbreak of that great catastrophe. In certain lectures are found subjects and investigations that were the direct outcome of war; the majority, however, have to do with conditions always present. It is a noteworthy fact that investigations of the latter nature were pursued in spite of the demands of Mars; a fact which augurs well for the future of the Society and the progress of Medicine in this country.

It is a source of regret that three of the lectures originally scheduled for this course are not printed in this volume. One on "The Food Supply of Europe During the Coming Year" was delivered by Dr. Alonzo E. Taylor, without manuscript; another "Approaches to the Problem of Schizophrenia (Dementia Præcox, so-called)," was not given because of the death of the lecturer, Dr. E. E. Southard. The loss of this lecture to the Society was little compared with the loss to our profession of one of its most brilliant investigators. The last lecture originally scheduled in this series was postponed until the next series, because the lecturer, Professor Jules Bordet, could not visit America until the autumn.

It is a pleasure to acknowledge the kindness of the Surgeon General of the United States Public Health Service, for his permission to print the lecture on Pellagra. We also wish to thank the editors of "The Archives of Internal Medicine," and "The American Journal of Children's Diseases," for permission to reprint the lectures that appeared originally in their journals.

HOMER F. SWIFT,
Secretary.

April, 1921.

THE HARVEY SOCIETY

A SOCIETY FOR THE DIFFUSION OF KNOWLEDGE OF THE MEDICAL SCIENCES

CONSTITUTION

I.

This Society shall be named the Harvey Society.

II.

The object of this Society shall be the diffusion of scientific knowledge in selected chapters in anatomy, physiology, pathology, bacteriology, pharmacology, and physiological and pathological chemistry, through the medium of public lectures by men who are workers in the subjects presented.

III.

The members of the Society shall constitute three classes: Active, Associate, and Honorary members. Active members shall be laboratory workers in the medical or biological sciences, residing in the City of New York, who have personally contributed to the advancement of these sciences. Associate members shall be meritorious physicians who are in sympathy with the objects of the Society, residing in the City of New York. Members who leave New York to reside elsewhere may retain their membership. Honorary members shall be those who have delivered lectures before the Society and who are neither active nor associate members. Associate and honorary members shall not be eligible to office, nor shall they be entitled to a vote.

Members shall be elected by ballot. They shall be nominated to the Executive Committee and the names of the nominees shall accompany the notice of the meeting at which the vote for their election will be taken.

IV.

The management of the Society shall be vested in an executive committee, to consist of a President, a Vice-President, a Secretary, a Treasurer, and three other members, these officers to be elected by ballot at each annual meeting of the Society to serve one year.

V.

The Annual meeting of the Society shall be held soon after the concluding lecture of the course given during the year, at a time and place to be determined by the Executive Committee. Special meetings may be held at such times and places as the Executive Committee may determine. At all the meetings *ten* members shall constitute a quorum.

VI.

Changes in the Constitution may be made at any meeting of the Society by a majority vote of those present after previous notification of the members in writing.

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CONTENTS

ILLUSTRATIONS

BIOLOGICAL STANDARDS AND THEIR APPLICATION IN MEDICINE *

GEORGES DREYER, C.B.E., M.A., M.D.

Fellow of Lincoln College, Professor of Pathology in the University of Oxford.

MR. CHAIRMAN, LADIES AND GENTLEMEN:

Before entering upon the subject of my lecture, I should like to express my great appreciation of the honor conferred upon me by your invitation to deliver one of the Harvey lectures.

It is with some hesitation that I have chosen a subject that might at first sight appear "academic." I hope, however, that if you do not at the present moment fully appreciate its practical bearings, that at least you will leave the lecture-room with a sense of sympathy with the views expressed, and even possibly with the feeling that the goal in view is not only worthy of achievement for itself alone, but is one which, if successful, will prove of the greatest importance to the future welfare of medical science.

The subject of biological standardization falls naturally under two main headings: (1) The aims and importance of standardization, and (2) the results already obtained by the adoption of certain standards.

In thus dividing our subject, we present to ourselves on the one hand the ideal to be attained, and on the other the tale of our present achievements, together with our shortcomings. Although our efforts in the past have so far yielded some definite results along these lines, there is great need not only for continued and unremitting effort on the part of individual workers, but also for the closest coöperation between scientists the world over before we reach the goal which will place the biological sciences on an equal footing with those hitherto accepted as "exact."

The first question that comes to the mind is: What advantages do we derive from the use of definite standard units? And the

* Delivered October 18, 1919.

answer is readily given—that scientific workers of every country and every race are able to understand each other for the simple reason that they "speak the same language." This has already been achieved in the field of electricity by the universal acceptance of the well-known standard units, the ampère, the volt, the watt, the ohm, etc., while the civilized world is still divided on such important questions as systems of weight, measure and coinage. Take, for example, the English-speaking peoples of the world clinging to the pound and the yard and the Fahrenheit scale, while the majority of other nations have adopted the metric system, admittedly superior for general as well as scientific use, and, incidentally, the invention of an Englishman who lived over a century ago.

If we now turn our attention to biological problems, the question of standardization becomes much more complicated, but certainly not less important. If we consider some of the obstacles that have hitherto barred the way, it is easy to understand why progress should have proved so slow. The difficulty of fixing a biological standard is only too often believed to be unsurmountable because of the idea so widely taught and accepted that any great degree of accuracy in biological science is beyond our reach. That this difficulty, however, is more imaginary than real should not be doubted when one remembers that some of the finest tests in the exact sciences depend on biological functions, namely, those of sight and hearing.

But to take the matter a step further—if a scientist devises a method for establishing a definite standard, he is at once confronted with the obvious difficulty of effecting a general adoption of his unit. This unwillingness to accept another investigator's standard is easily understood. It arises from the fact that "individuality and independence" is the proper spirit in science, and any measure that might tend to interfere with that freedom of thought and action is justly condemned. And as the acceptance and use of a biological standard often impose the adoption of a definite technic, one easily understands the hesitation.

Nevertheless, it will be profitable to approach the subject from another point of view and to ask whether the use of a valid stand-

ard unit can ever really interfere with individual freedom. My personal answer is in the negative. Hardly anyone, even the greatest of champions for individuality, would maintain that the universal acceptance of units, like the ampère, the volt and the ohm, has in any possible way interfered with the individuality and originality of modern investigators. On the contrary, research carried out without the use of these standard units would be lost to the scientific world at large because of the lack of information concerning the values involved.

Another objection to biological standards to which prominence is frequently given is that they are merely empirical and arbitrary units. But in this respect certainly they do not differ from any unit already in use, be it weight, measure or degree. It is, therefore, evident that the importance of developing valid biological units cannot be exaggerated.

Biology, as well as any other science, during its development must necessarily pass through the qualitative into the quantitative stage. But quantitative experiments, capable of repetition and reproduction, are dependent upon the use of a unit system. If every worker should establish his own unit system, he would deprive other workers in the same field of the benefits of his experience and researches, while if he should express his findings in terms of a universally known system his conclusions could readily be verified and extended by other investigators along similar lines.

Let us for a moment consider what it would mean to medical science to be able to express in sound and valid units the findings of clinical tests like the Wassermann reaction for syphilis or the Gruber-Vidal agglutination test for enteric fevers, and contrast it with the difficulties which obtain at the present moment, when the results from one laboratory, quantitatively considered, cannot be compared with those from another institution in the same city and therefore even less with those produced in a different country.

Taking it for granted that the establishment of standard units is highly desirable, or even necessary, to enable us to compare results obtained at one time and place with those secured at other times and in other countries, we are faced with the problem of

what should constitute valid and useful standards. So far as I can see, there are no great difficulties in laying down rules in this respect that would meet with general approval: (1) The established standard unit must be easy to maintain and check. (2) The technic involved in its application should be simple and accurate. (3) In vitro tests should be preferred to animal experiments. (4) It is highly desirable that one should be able to determine the number of standard units per cubic centimetre or gram no matter whether absolute quantities or relative proportions are made use of in the test.

Having already dealt at some length with the aims and importance of biological standardization, we will now consider the results thus far attained. In this connection we should not forget the debt of gratitude we owe to the pioneer workers in the field of immunity and serum therapy, of Pasteur, Roux, Behring and Ehrlich.

The fact once established that certain infectious diseases, diphtheria, for instance, could be successfully treated by the administration of antitoxins, there immediately arose the necessity for developing an antitoxin unit to enable one to give definite doses of the active substance. For otherwise it would be impossible to draw sound conclusions as to the results of treatment. After extended experiments, Ehrlich succeeded in establishing a standard unit for the measurement of the strength of diphtheria antitoxin, which has, step by step, won the favor of the medical profession and is now in use throughout the civilized world.

Units based on similar principles have been worked out for the serum treatment of tetanus and pneumonia, though they have not achieved the same degree of success.

Similar attempts have been made to standardize certain drugs, notably digitalis, pilocarpine, adrenalin and salvarsan.

As regards the working out of definite unit systems for diagnostic tests, we have made but small progress, and much spadework must be done before the importance of advance in this field is realized.

But surely in the true interests of medical science there can

be no doubt that units which allow investigators to compare their results quantitatively with those of other workers in other countries cannot be valued too high. Attempts in this direction have already led to practical results in the diagnosis of enteric fever, dysentery and cholera by the agglutination test through the introduction of standardized agglutinable cultures, enabling us to express the agglutinating power of a given serum in terms of a definite unit system. In this connection, think of the immense advantage to the physician of a diagnostic test for syphilis that would enable him to follow the results of modern treatment by repeated examinations of the patient's blood, expressing his findings in terms of a unit system so that they could be quantitatively compared from day to day and from week to week.

From a practical point of view it is extremely important to adopt the same standards in all countries, for with the development of medical science and the treatment of various diseases by means of antitoxins and vaccines, it naturally follows that commercial firms will more and more interest themselves in the preparation of these products, and if there exists no international agreement to secure identical products being marketed in the different countries, the country with the lowest standard of excellence will perforce receive all preparations rejected in the countries where the standard is high.

The time is therefore ripe for the establishment of not only national but also international standardization committees which would carefully examine and test new units developed by scientists of all nations and finally agree upon and accept those of proven worth.

Undoubtedly great strides could be made towards the attainment of this ideal if the two great English-speaking nations, working together, should lead the way. Let us, therefore, hope that we may soon accomplish for scientific medicine what has already been done in the field of physics, and that the time has nearly arrived when we shall see biological standard units as firmly fixed as the ampère, the volt and the ohm.

"THE NATURE AND CAUSE OF WOUND SHOCK" *

H. H. DALE, C.B.E., M.D., F.R.S.

Head of the Department of Biochemistry and Pharmacology, under the Medical Research Committee, London.

I HAVE felt it a very great honor to receive, across the Atlantic, an invitation to address this Society, which, in its very name, emphasizes the community of tradition in medical science which is the heritage of all who speak the language which Harvey spoke. Your president, in his very kind letter of invitation, did me the further service of indicating that you would be willing to hear me lecture on shock. I gladly adopt that suggestion; for the subject is one which has been prominent in the interest of my immediate colleagues and myself during the past few years, and it is one in connection with which we English workers owe a debt beyond all acknowledgment to the American colleagues who came over to help us with their coöperation in the time of our national need.

I feel impelled, however, to say a word of apology and disclaimer. As a mere laboratory worker I know nothing at first hand of shock as a practical clinical problem. I can only attempt to deal, mainly from the experimental standpoint, with one aspect of a very big subject. Indeed, the subject is so vast and so ill-defined, that I doubt whether the most highly qualified exponent could cover the ground in the space of a lecture. I think I shall make the best use of the time at my disposal if I try to give you a brief account of what we, your countrymen as well as mine, tried to do on the other side of the Atlantic towards investigating the nature of the condition which came to be called "wound shock" during the war; not, by any means, because I regard it as more important than what was done here in America, but simply because I think you would wish to hear me speak of that with

* Delivered November 8, 1919.

which I have been closely connected, rather than of what many of you know better than I do.

During the fifteen or twenty years preceding the war surgical shock had been vigorously and fruitfully investigated, predominantly by American surgeons and physiologists; and whatever may be thought concerning the permanent validity of some of the theoretical conclusions put forward, I think it can hardly be doubted that this concentration of interest on the problem had a splendid practical result. Just as Lister's work had led to developments, which largely freed surgery from the horror of sepsis, so, in turn, the physiological peril of operation was rapidly disappearing under improved technic. I think it is hardly too much to say that the day was in view when serious shock, following operation through healthy tissue, would be as much a reproach to the surgeon as suppuration under the same conditions had already become.

Then came the war, which seemed to destroy the basis of all calculation and the value of all experience. In the early days the cry arose that the practice based on Lister's work was powerless to deal with the lacerated wounds, impregnated with a highly cultivated soil, which the surgeons were called upon to treat. Later, when the lines became relatively stabilized, and when wounded men, who in the early days would mostly have died in transit to the base, came under treatment at the casualty clearing stations, the surgeons were faced with a high proportion of deaths from a condition which they identified with the shock, which better methods had so largely succeeded in banishing from the theatres and wards of the civil hospital.

It came to the notice of the Medical Research Committee in London, under which I have the honor to serve, that several experimental workers in England were engaged in investigations which seemed to have some bearing upon this condition, and they realized the desirability of bringing these different workers into touch, and of coördinating their effort with that of surgeons working at the clearing stations in France. A small committee was, therefore, appointed, consisting of physiologists kept in England by other duties and of surgeons dealing with practical

problems in the field. Of this Special Investigation Committee, Professor Starling was the first chairman, Professor Bayliss succeeding him at a later stage. Professor Cannon was already in France and joined the committee at its formation. Professor Richards, whose personal coöperation alone made it possible for me, in the midst of other duties, to take any part in the work, came over a little later, for the special purpose of putting his skill and experience at our disposal. The fact that I acted as secretary to this committee is my chief justification for speaking to you on this subject, and I am going to try to give you a brief history of that part of their activities which was concerned with an attempt to define the nature and determine the cause of "wound shock." Our reference was of the widest kind; we were to find out all we could concerning shock and allied conditions, with the object of helping the surgeons in the army to improve their methods of prevention and treatment. In the time at my disposal I can touch only briefly on the measures recommended and the degree of success obtained by their application. These are set forth in the Medical Research Committee's Special Reports, Nos. 25, 26 and 27.

I must confine myself chiefly to the questions of the nature and cause of the condition. We began by trying to arrive at a consistent definition of "shock." We failed, and I believe we were bound to fail. I do not think there is room for doubt that the word "shock" has been very loosely applied. Such definition as we could obtain seemed to be reached by a process of exclusion. The term seemed to have been applied to any condition of depressed vitality, with a circulatory deficiency as its central feature, provided that it developed fairly rapidly and that no hemorrhage or infection adequate to account for it had been recognized. I say "recognized" advisedly. I believe there have been many cases labelled "shock" in which loss of blood has played a far more important part than the surgeon has realized. Captain Bazett made for us some accurate estimations of the blood lost in lotion and on sponges, in a group of operations in France, which the surgeons regarded as quite normal in respect of hemorrhage. The results were surprisingly high. I believe that many

cases have been called "shock" during the war, in which unrecognized septic infection was present. But every one seems to be agreed that there was a large residuum of cases in which some other unknown factor was at work, which for want of better knowledge was called "shock." It seemed possible, therefore, that a number of different conditions, different in origin and possibly even in their physiological nature, were included under the term shock as used by different authorities, or even by the same authority at different times. In one direction this is more than possible. There can be no doubt that the name shock has, at different periods, been applied to different conditions.

By "shock" the earlier writers meant a sudden, often fatal, prostration following immediately on the receipt of a painful injury not directly involving any vital organ. Its difference from the ordinary, simple fainting-fit is apparently chiefly in severity, and it would be impossible to draw a clear line between the two. You are all doubtless familiar with the old experiment of Goltz, which seems to have given an adequate picture of the physiological nature of this condition. You will remember how he suspended a frog and tapped the exposed viscera with a flat instrument. The heart was arrested by reflex inhibition, and the vessels in the splanchnic area suffered a reflex inhibition of their tone, so that a large part of the blood collected in them by gravity. When the heart began to beat again, therefore, it was almost empty. It was, at least, for the most part, this suddenly developing condition, due to reflex inhibition, which the earlier writers called "shock"; and the term, with its suggestion of a sudden effect of violence, had some appropriateness. A more slowly developed and progressive depression of vitality, similar to that associated with a rapidly generalized infection, was more usually called "collapse."

Later the application of these terms seems to have become inverted. Crile, in particular, has applied the term "collapse" to the sudden inhibition which his predecessors called "shock," reserving the "shock" for the more slowly developing, persistent and progressive condition. And it is this latter form of circulatory failure, which, under the name of shock, has been the subject of most of the experimental investigations of recent years.

The same two conditions were early differentiated by surgeons in France. They employed yet another variation of the nomenclature, calling both "shock," but speaking of the state of sudden unconsciousness, with slow, weak heart-beat and feeble pulse, occurring almost immediately after receipt of a wound, as "primary wound shock," and calling the condition of later and slower onset, with little tendency to spontaneous recovery, "secondary wound shock." I believe Colonel Cowell first definitely made this distinction. The primary wound shock yielded to simple restorative measures at the dressing stations and created no serious problem. Captain Walker represented to us its significance as a protective reflex, restricting the peripheral circulation until severed arteries had contracted and become occluded by clot, and thus limiting hemorrhage.

It was the later condition, the "secondary wound shock" developing some hours after receipt of an injury, while the patient was in transit to a clearing station or after his arrival there, which was causing heavy loss of life among men whose wounds, from the purely surgical aspect, presented no hopeless problem. This was the condition we were urged to investigate, in order that means of prevention or remedy might, if possible, be found.

It presumably corresponded to, or was included in, the shock which had been the subject of so much investigation during the past twenty years. But concerning the nature of this, also, a study of the literature revealed a fairly sharp division of opinion among those who had investigated it experimentally. There was agreement on some main points. It was agreed that the defect of the circulation, which formed a central feature of the condition, was not due to primary weakening of the heart's activity, but to a reduction of its output, owing to defective filling from the veins. Crile attributed this to exhaustion of the vasomotor centre, as the result of persistent overstimulation by afferent impulses. This was pictured as causing general relaxation of arterial tone, particularly in the splanchnic area, as a result of which a large part of the blood was supposed to accumulate in the large veins of the abdomen, so that the filling of the heart was defective. Mummery and Symes, adopting this conception, pro-

duced experimentally a condition which they regarded as corresponding to ''shock,'' by destroying the whole central nervous system in cats. They laid some stress on a feature of the condition so produced, which came to have a certain importance; as always under conditions of low blood pressure produced by arterial relaxation, there was an attempt at compensation for the increased capacity by absorption of water from the tissues; the blood became more dilute and its corpuscular content fell.

We may take as the characteristic features, then, of the condition as so conceived, a loss of arterial tone, an overfilling of the great veins, and a dilution of the blood. On all these points it is sharply contrasted with another conception of the condition. Sherrington and Copeman some years earlier had observed a concentration, or inspissation of the blood, with rise in its corpuscular content, in experimental shock, and Malcolm had observed the same phenomenon in clinical, post-operative shock. Malcolm also maintained that the arteries were constricted. This same combination of arterial constriction and rise in corpuscular content of the blood figures in the circulatory aspect of shock as described by Yandell Henderson, and by Mann of the Mayo Clinic. Seelig and Joseph, also, had meanwhile given experimental evidence that the vasomotor centre, so far from being exhausted, was abnormally active in experimental shock. In the picture, as drawn by Henderson and by Mann, the veins also were abnormally empty. Henderson attributed the failing circulation to defective venous pressure, which he found to be in some way associated with excessive removal of carbon dioxide from the system. Mann, without committing himself to a definition of the exact cause, gave a very striking description of the condition, which he produced by manipulation of the bowels—constricted arteries, veins and heart depleted of blood, concentrated blood, obviously deficient volume of blood in effective circulation. He found that the residuum of blood which was left in the body, when the animal was ensanguinated by opening the large arteries and veins, was much greater in shock than in the normal animal. There were thus two clearly divided conceptions of the state of the circulation in shock. Both agreed that the lowering of blood

pressure was due to defective filling of the heart. But, on the one hand, Crile and his followers maintained that the arteries were relaxed, the veins full, the blood diluted; while Henderson, Mann and others maintained that the arteries were constricted, the veins abnormally empty, the blood concentrated, and the volume in effective currency greatly reduced. Incidentally, I may mention here a matter to which I will return later. Laidlaw and I, in studying the shock-like condition produced in the cat by injecting the base ''histamine,'' a highly active amine derived from the amino-acid histidine, had found it to correspond closely with the shock described by Henderson and by Mann; the output of the heart failed from lack of blood to propel, though the arteries were constricted and the veins abnormally empty; the blood was concentrated by loss of its plasma; and we had reached the conclusion that the main factor in the gross defect of blood in effective currency, the pronounced ''oligemia,'' was a loss of the normal tone of the capillary vessels all over the body, associated with such abnormal permeability as allowed the plasma to leave the vessels and pass into the tissues.

We were able, then, to present this definite issue to the surgeons studying ''secondary wound shock'' in France. Did the features of the condition correspond to those of the vasomotor exhaustion of Crile and Mummery, or to those of the oligemia described by Henderson and Mann, and reproduced in the shock-like condition caused by histamine?

The question was easy to put, but not so easy to answer. Remember that almost every case had suffered from a more or less serious hemorrhage; it took much care and experience to discount the effect of this in reaching a conclusion as to whether the shock was attended by dilution or concentration. Fortunately surgical was reinforced by physiological skill and experience, since Colonel Cannon had joined Sir Cuthbert Wallace and his enthusiastic team at Bethune. Gradually the turbid suspension of opinion began to clear and crystallize into definite conclusions. We were informed that there was no perceptible congestion or accumulation of blood in the abdominal vessels; that the arteries everywhere seemed to be constricted, both they and the veins

being abnormally empty; that when allowance was made for the effect of hemorrhage, the corpuscular content of the blood was abnormally high, in many cases above the healthy normal in spite of hemorrhage, and especially higher in the superficial capillaries than in the veins; that the heart was beating fast and vigorously, and continued to beat after the respiration failed, but that the patient was pulseless because there was a grossly inadequate volume of blood for it to propel. Later Captain Keith, by application of his vital red method, gave direct demonstration of the defect in the volume of blood effectively circulating.

So that, whatever might be true of the shock of civil practice, the condition which the surgeons in our army called "secondary wound shock" seemed to correspond in every respect with the oligemic condition obtained experimentally by Henderson and Mann, and with the shock-like condition which we had found to be produced by histamine. Cannon, in his study of wound shock, was forced, as Laidlaw and I had been, in our experiments with histamine, to account for a greater deficit of blood volume than the loss of plasma, indicated by concentration, would explain. As we had done, he located the missing blood in slack and dilated capillaries. The condition being thus fairly well defined, we had to turn our attention to its cause. Practically nothing was known of a nervous control of capillary tone. The brilliant work recently published by Krogh arouses hope that such knowledge will not remain permanently beyond reach. For the time being, however, we had to consider other possibilities. I have already reminded you that Yandell Henderson had attributed the very similar condition, which he produced experimentally, to excessive removal of carbon dioxide from the system and suggested that clinical shock was due to this cause, owing to the overactivity of the respiratory centre produced by pain. I do not propose to enter into the general question as to whether lack of carbon dioxide can produce such a condition. The practical point for us was that this conception involved the assumption of dyspnœa preceding and determining the onset of the shock, and that the most careful inquiry and directed observation failed to produce any evidence of this in the wounded men; the surgeons were

positive in their assertion that it did not occur, and I do not think they could have missed it if it did.

I must make brief mention of acidosis. As many of you have probably read, Cannon, during his stay at Bethune, was much impressed by the association between wound shock and a fall in the bicarbonate, the so-called alkali-reserve of the blood plasma, as determined by Van Slyke's method. His success in carrying through a long series of observations on this association under the conditions of a clearing station speaks volumes for his enthusiasm and enterprise. Those of us at home who, from the first, felt doubtful of its causal significance, sympathized fully with his eagerness to grasp at any possible factor in the condition which held out hope of easy remedy. Our committee, as I have mentioned, had the advantage of numbering Professor Cannon and Professor Richards among their members, and we had a friendly controversy over this question of the significance of acidosis in shock; but the only point that now matters is that we ultimately became unanimous in our conviction that, though acidosis was a feature of wound shock, it was a consequence and not a primary cause of the failure of the circulation.

The time spent in examining the significance of this acidosis was not wholly wasted, however. Experiments made in connection with it had, at any rate, provided evidence that a chemical factor was concerned in the production of a shock-like condition following injury. Bayliss and Cannon had taken cats, anæsthetized with urethane, and had inflicted massive injury on the thigh muscles by crushing them with blows of a hammer. Little hemorrhage was thus produced, but the animals passed into "shock," even if the nervous connection of the lower limbs with the rest of the system had been broken by cutting the spinal cord in the lumbar region. On the other hand, if the nerves were intact but the limb vessels were clamped, no shock appeared until the blood was readmitted to the injured tissues. Something was apparently being absorbed from the injured muscles which was concerned in the production of shock. At the time the experiments were made, it was considered possible that this was lactic acid; but that theory was disposed of to the general satisfaction. Bayliss found

that the shock so produced was not relieved by injection of sodium bicarbonate; indeed, some of his experiments seemed to show that injections of lactic acid did more good. But some evidence had, at least, been obtained in favor of a chemical, rather than a nervous agency, as a factor of central importance in the production of the condition we were studying, and attention was attracted to another kind of chemical agency, the significance of which had meanwhile become more apparent.

I have mentioned already the shock-like effect of large doses of histamine. This substance had long been known to have a depressor action, due unmistakably to vasodilatation, although outside the body it had an intense stimulant action on all kinds of plain muscle, including that of the arteries. The arrival of Professor Richards made it possible to resume the investigation of this paradox, and the experiments which his fresh view of the matter initiated soon led us to the definite conclusion that the vasodilator action of this substance *in vivo* was due to a general weakening, not of arterial, but of capillary tone, and that histamine, in big enough doses to affect the arterial plain muscles, caused constriction of the arteries in the living body as in the surviving and separated organ. The meaning of the shock-like action of larger doses which I had studied with Laidlaw began to be clear. We supposed that, under normal conditions, only a small part of the available capillary network throughout the body is at any one moment functioning as a channel for the blood, most of the capillaries being contracted even to closure; that the flow is constantly shifting from one portion of the network to another, though the average available field remains approximately constant; but that, when all the capillaries become simultaneously relaxed and patent under the influence of a sufficient dose of histamine, the total capacity becomes such that a large part of the blood soaks into the tissues as into a sponge. The simultaneous contraction of the arteries cannot prevent this; it merely holds up the arterial pressure, so that it falls slowly as the output of the heart, with the failing venous return, gradually falls to very small dimensions. Meanwhile, the defect of blood volume is accentuated by the passage of plasma out through the slack and poisoned endothelium of the capillaries.

Now this action reproduced the characteristic features of and provided a rational explanation for the kind of circulatory failure which formed the central feature of wound shock. Indeed, it is hardly too much to say that, if the condition in wound shock is due to a chemical substance passing into the blood from injured tissues, it must be a substance having this type of action. There is reason, further, for supposing that, when tissues are killed and autolysis begins, products having this type of action are actually liberated. They can be extracted from most tissues of the body, or produced by partial digestion of any protein, or by bacterial action. Professor Abel has recently published evidence which leads him to the conclusion that the active substance thus liberated, when tissues are injured or proteins partially digested, is either histamine itself or some substance having a close chemical relation to it. His evidence is admittedly incomplete at present, though highly suggestive. For our present purpose it does not matter whether histamine itself is liberated from injured tissue; it is sufficient to know that something having this type of action is produced.

This experimental suggestion of the importance in wound shock of such toxic substances was soon reinforced by clinical evidence. Early in our inquiry Sir Cuthbert Wallace had drawn attention to the prevalent association between shock and injuries of large muscle masses in the limbs, or multiple wounds of the trunk muscles. French surgeons, Quénu and Delbet, who had independently followed the same clue, showed that arrest of the circulation to a wounded part by pressure would prevent the appearance of shock, which appeared, however, when the blood was readmitted to the damaged tissue. McNee, of the British Medical Service, made a similar observation, and was careful to exclude hemorrhage and sepsis as factors in the cases which he studied. Later similar observations were made by Cannon, when he returned to France with the American army.

Our committee thus reached by several different lines of approach the conception of a *traumatic toxæmia* as a central factor in the oligemic condition, the "secondary wound shock," which they were called upon to study. The conception brought

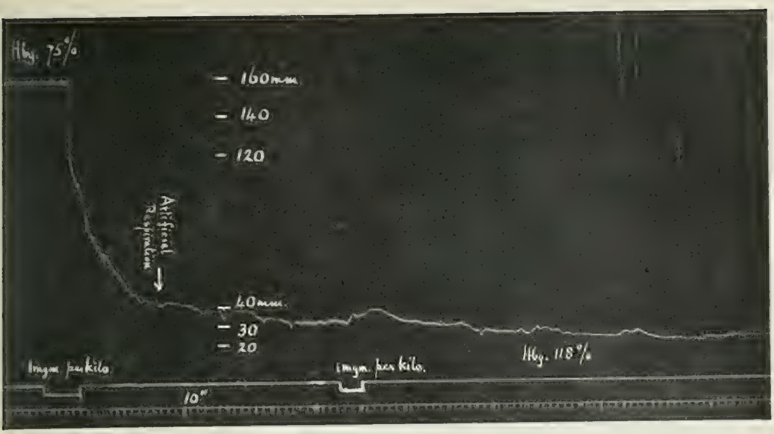

Fig. 1.—Arterial blood-pressure of a cat after two hours under ether. Effect of 2 milligrams of histamine per kilogram intravenously (given in two doses). Note the permanent fall of blood-pressure (from which there was no recovery), the obliteration of the pulse waves, and the loss of plasma, indicated by rise in hæmoglobin value of the blood from 75 to 118 per cent.

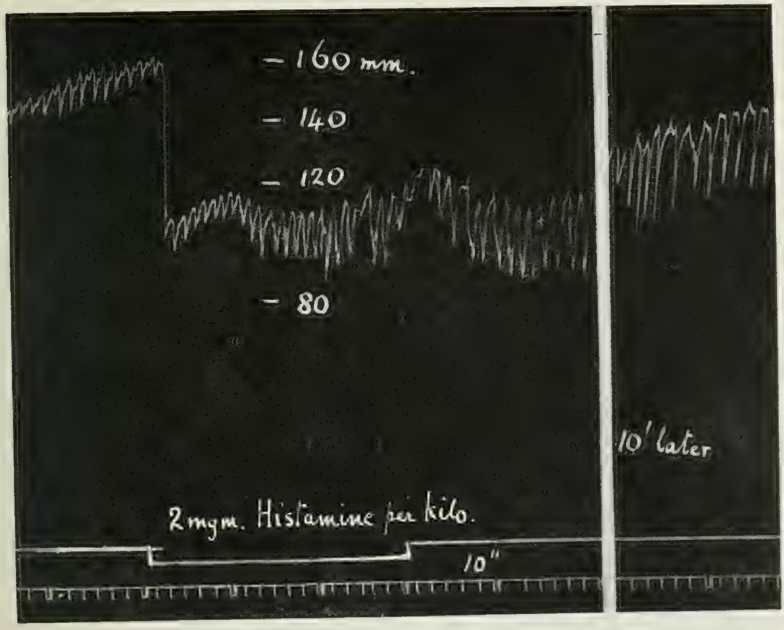

Fig. 2.—Arterial blood-pressure of a cat after one and a half hours under nitrous oxide and oxygen. Effects of 2 milligrams of histamine per kilogram intravenously. Note the evanescent and small fall of blood-pressure, with no serious diminution of cardiac output.

this type of shock into relation with the state of collapse produced by a severe generalized infection, from which, indeed, it could only be differentiated with certainty by excluding the factor of sepsis. On general principles I think this might have been expected. An infection which, if locally restricted, produces the phenomenon of inflammation—dilatation of capillaries, concentration and tendency to stasis of the blood, permeability of capillary walls leading to œdema and swelling—if rapidly generalized leads to a profound circulatory collapse, due, as we suggest, to generalized relaxation of capillary tone. Similarly a local trauma, not severe enough to rupture blood-vessels, causes local redness, followed by the formation of an œdematous wheal. Histamine applied locally to the lightly scarified skin has the same effect, as Sollmann and Pilcher have shown. Analogies were not wanting, therefore, to support the supposition that a rapid generalization, of the effects produced by the products of tissue injury, would lead to the production of a condition such as that which we were called upon to study.

There remained the important question, whether we should be justified in regarding such a traumatic toxæmia as the only important factor in the production of the state of wound-shock. I think not. If we can safely take histamine as a type of the substance produced by injury, the answer would be "certainly not." The experimental effects which I have been describing were all obtained in animals anæsthetized with ether, or some similar anæsthetic, or by decerebration. Under such conditions 1 or 2 milligrams of histamine per kilogram will produce an irremediable shock. But, if this base is slowly run into the vein of a healthy unanæsthetized cat, relatively very large doses—certainly up to 10 milligrams per kilogram—can be tolerated with only slight evanescent symptoms. And the same is true if, instead of ether, we use nitrous oxide and oxygen as the anæsthetic. Figs. 1 and 2 illustrate the contrast between the effects of 2 milligrams of histamine per kilogram on the arterial pressure of cats anæsthetized with ether and with nitrous oxide and oxygen respectively.

There is here a very suggestive reminiscence of the experience of surgeons in France. They found that a man, severely wounded but apparently in fairly good condition, was often pushed on to

the downward slope, and passed into fatal shock, as the result of giving ether or chloroform for some necessary operation. More and more these anæsthetics were abandoned in favor of nitrous oxide and oxygen for such cases, whenever these could be obtained. The fact that Doctor Crile, by quite a different line of observation, has been led to replace ether by nitrous oxide where possible in civil surgery, may have some significance in this connection. A preliminary hemorrhage again, not in itself severe enough to imperil the animal's life, or greatly to impair its apparent vigor, makes it incapable of resisting one-tenth of the dose of histamine which it would normally tolerate. Cats from which the suprarenal glands have been removed, but showing as yet no signs of impending death, I have found extremely sensitive to histamine, very small doses of which have proved rapidly fatal.

There are many other factors calculated to depress a normal resistance, which are less suitable for experiment on animals. Cold, thirst, exhaustion were almost regular complications of the condition in the wounded man. A reduced volume of blood in circulation throws an extra strain on the vasomotor centre, which is called upon to maintain a sufficient arterial pressure to ensure an adequate supply of blood to the vital nerve centres. It is hardly to be doubted that the excitement and physical strain of battle, the prolonged pain and emotional stress of transport to hospital, would weaken the power of the vasomotor centre to respond to this additional call. All such factors—anæsthesia, hemorrhage, suprarenal exhaustion, cold, lack of fluids, vasomotor fatigue—with which Crile's writings have made us so familiar, may freely be allowed to have had importance as tending to impair the natural resistance, the normal power of dealing with the toxic products of injury. They were the more important as being to some extent controllable; and it may be said that efforts to prevent shock, by measures designed to keep the patient warm, to supply abundant water, to immobilize injured parts during transport, were much more successful than the treatment of the developed condition.

For the latter, in which the effective blood volume has already become seriously diminished, the only hope would seem to lie in restoring the volume of the circulation by transfusion of blood

or, failing that, infusion of a substitute such as the saline gum acacia solution devised by Bayliss. Too often, however, it appeared that, when once the shock had become fully established, the capillary walls were so seriously damaged that such fluids, and even blood, produced only temporary improvement, and the circulating volume soon sank to its previous low level. In this respect wound shock differed from the effects of simple hemorrhage. Superficially the condition due to loss of blood from effective circulation naturally showed great resemblance to that produced by loss of blood from the body by hemorrhage. But the latter was readily relieved by transfusion of blood, or of an artificial fluid which the vessels would retain; in proportion as the element of shock preponderated over that of hemorrhage, in proportion, that is to say, as the toxic loss of capillary tone became prominent in the picture, the prospect of recovery under treatment grew worse.

I have spoken, I fear, at unreasonable length of an investigation dealing with one particular condition to which the name "shock" has been applied. I should like again to emphasize the fact that I make, for the conclusions I have put before you, no claim to give an explanation of shock in general. We return to the point from which we started. The word shock, I suggest, is used, by surgeons and experimental workers alike, for a number of different conditions, having probably different origins, but presenting certain features in common. Shock, as yet, is not so much a clinical entity as a dumping ground. Gradually we ought to be able to rescue from this scrap heap one well-defined clinical or pathological entity after another. I have endeavored to put before you one such effort at salvage; but I should deprecate any attempt to assume that what we were able to study is the true shock, and that all other claimants to the title are imposters. It may well be that in the shock of civil surgery nervous effects will be found to play a greater part than that which we are led to accord to them in the wound shock of war. One is forced to hope that the opportunities for clinical study of the condition will become ever more rare, but that the use made of them for investigation will increase in inverse proportion to their abundance.

CHEMISTRY OF THE THYROID SECRETION *

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DURING the past thirty years many reports have been published concerning the clinical symptoms, the surgery and pathologic conditions associated with thyroid disturbances. To-night I wish to present some facts which have resulted from a chemical investigation of this gland. In 1895 Baumann directed the attention of chemists to the thyroid by announcing the discovery that iodine is a normal constituent of the gland. This finding stimulated a large amount of chemical research, and Baumann himself succeeded in concentrating the iodine compounds of the gland until a certain portion contained about 9 per cent. of iodine. This mixture of compounds Baumann named iodothyrin, and for some time iodothyrin was regarded as the active constituent of the thyroid. Of late,[15] however, this claim has been brought into doubt, and to-day iodothyrin is not looked upon as even a concentrated form of desiccated thyroid.

Just after Baumann published his work, Oswald separated the proteins of the thyroid and showed that the portion containing iodine possesses the physiologic activity of the entire gland. This fraction he called thyreoglobulin. Among the important results of his work three facts especially may be pointed out: (1) The substance producing the physiologic activity does not exist in free form, but is an integral part of the thyroid proteins; (2) the physiologic activity of thyreoglobulin is not easily destroyed; and (3) the activity of thyreoglobulin appears to be proportional to its iodine content.

Other investigators have isolated products from the thyroid which contained iodine, but they were all similar in nature to thyreoglobulin. The proteins of the glands have also been digested with pepsin and pancreatine,[7] and iodine-containing compounds have been separated in the form of mixtures, but none

* Delivered December 13, 1919.

of these has contained a very high percentage of iodine. The chemical investigation of the thyroid up to 1914 had resulted, therefore, in the separation of two types of products, one obtained by merely fractioning the proteins without any deep-seated destruction, and the other the result of acid hydrolysis of the proteins yielding iodothyrin.

It is to be noted that Baumann used an acid for the destruction of the thyroid proteins, and, although this treatment broke down the proteins, it also destroyed the physiologic activity of the resulting material. The fact that the iodine compound is firmly held within the protein complexes of the thyroid secretion showed that some method of hydrolysis would be required to liberate the compound before any attempts at isolation could be successful. For this reason some other method than acid hydrolysis for liberating the iodine compound from the proteins seemed necessary. I, therefore, decided to investigate the effect of alkali on the thyroid proteins and the iodine compound, although recognizing the fact that almost all organic compounds containing iodine are easily broken down by sodium hydroxide, and the iodine is split off in inorganic form.

Dilute sodium and barium hydroxides were used at first, and a certain amount of hydrolysis was produced. Further investigation showed that the iodine compound is remarkably stable toward alkali and can withstand severe treatment. This eventually led to a breaking down of the proteins in 90 per cent. alcohol with 2 per cent. sodium hydroxide.

In its resistance to alkali the iodine compound of the thyroid is probably unique. It cannot be destroyed by any amount of sodium hydroxide at room temperature; even the strongest solutions will break off only traces of iodine as sodium iodide.

Since acid hydrolysis of the proteins destroyed the physiologic activity of the gland and since treatment with sodium hydroxide did not break off the iodine, it was decided to investigate further the result of treating the thyroid proteins with strong alkali to determine whether or not a method could be based on this type of hydrolysis. It was found that the products resulting from the treatment of the thyroid proteins with sodium hydroxide could be separated into two groups, one soluble in acids and the other

insoluble, and it was soon established that the acid-soluble constituents are without physiologic activity. The acid-insoluble constituents, on the other hand, possess the physiologic activity of desiccated thyroid. In November, 1914, desiccated thyroid was purified by treatment with alkali, followed by further removal of impurities with barium hydroxide until the iodine content was 26 per cent.[8] During December, 1914, the purification was pushed still further, until a mixture containing 43, 47 and finally 60 per cent. of iodine was obtained, and on Christmas Day, 1914, the compound was first obtained in pure crystalline form. This was the first isolation from the thyroid of a single crystalline compound containing iodine which possessed physiologic activity.[9]

After isolation of the substance no difficulty was anticipated in repeating the work and separating any desired amount. In order to enlarge our facilities a galvanized iron tank was used instead of glass flasks for treating the thyroid proteins with alkali. After six months' failure to separate more of the compound, it was eventually shown that the presence of all metals, except nickel, gold, silver and platinum, destroys the iodine compound. Besides this destructive action, due to the presence of metals, there were other factors which prevented its separation, and fourteen months of continuous effort were required to overcome the difficulties which had prevented the isolation of more of the iodine compound. At last all of the difficulties were appreciated, if not overcome, and a method was finally evolved which permitted the isolation of sufficient of the compound to establish its chemical nature and physiologic activity.

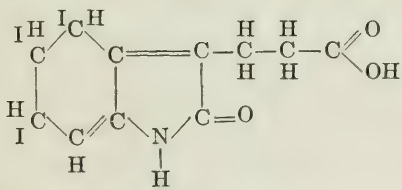
In 1917, after the accumulation of about 7 gm. of the crystalline iodine-containing compound of the thyroid, its chemical formula was determined. Since that time we have made derivatives confirming the structural formula assigned and have used a large amount of the material in the clinical treatment of hypothyroidism. Altogether approximately 36 gm. have been isolated from three and one-half tons of fresh thyroid glands, principally of the hog. The substance has been named thyroxin.

Thyroxin is a white, highly crystalline substance, odorless and tasteless. It may be separated from aqueous or alcoholic solutions

in microscopic crystals, which are not soluble in any organic solvent, except those which are strongly basic or acidic in nature. It is soluble in alcohol in the presence of mineral acid or an alkali metal hydroxide. It is stable toward heat; and its melting point is in the neighborhood of 250° C. Since it is odorless and colorless and is not easily affected by oxidation and reduction, its most important chemical and physical properties are concerned with the acidic and basic groups within the molecule. Thyroxin is a weak acid, but possesses basic properties in the presence of mineral acids.[10]

Thyroxin is a derivative of indol and possesses to a high degree the peculiar tautomeric properties of certain members of this group of compounds. In acid solutions it exists with an imino-carbonyl linkage. In alkaline solutions the hydrogen of the imino group migrates, forming an enol structure. Beside these tautomeric forms thyroxin has the power of adding the elements of water to the pyrrol ring and existing in an open-ring structure. With this structure there are also two tautomeric forms, to which may be added the organic salts formed with the amino group. The proof of these structures is given elsewhere, but it is essential in a consideration of the physiologic activity of the substance to understand the chemical properties which are present in the molecule (Figs. 1 to 6).

FIG. 1



4, 5, 6 tri-hydro-4, 5, 6 tri-iodo,-2 oxy,-beta indolepropionic acid.[1]

Fig. 1.—The formula of thyroxin in keto structure.

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[1] In this paper the positions in the indole nucleus will be referred to as follows:

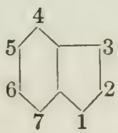

Fig. 2

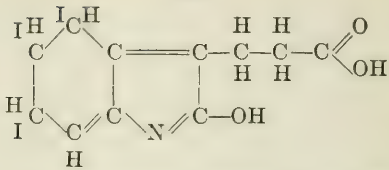

Fig. 2.—The formula of thyroxin in enol structure.

Fig. 3

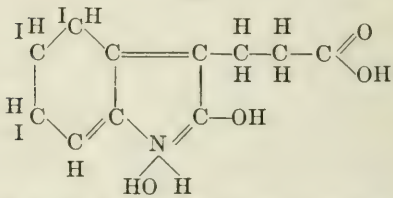

Fig. 3.—The formula of the amino hydrate form of thyroxin. This is made by the addition of the elements of water to the enol structure.

Fig. 4

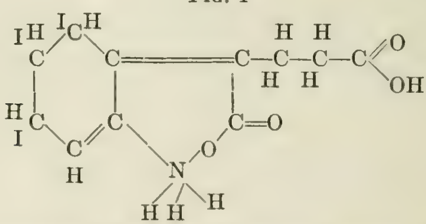

Fig. 4.—The formula of the amino carboxyl structure of thyroxin.

Fig. 5

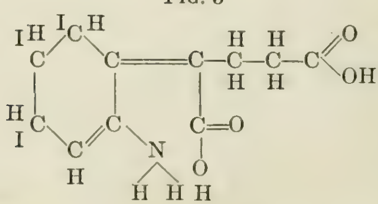

Fig. 5.—The formula for the open-ring structure of thyroxin.

Fig .7.

Fig. 8.

Fig. 7 (237778).—Appearance of patient upon entering the clinic.
Fig. 8 (237778).—After eighteen days' treatment, during which time the patient received a total of less than 25 mg. of thyroxin.

Fig. 9.

Fig. 10.

Fig. 9 (127778).—Appearance of patient upon entering clinic.
Fig. 10 (127778).—After eighteen days' treatment, during which time patient received a total of less than 25 mg. of thyroxin.

Fig. 11.

Fig. 12.

Fig. 11 (146434).—Appearance of patient upon entering the clinic.
Fig. 12 (146434).—After twenty-four days' treatment, during which time the patient received thyroxin.

Fig. 6

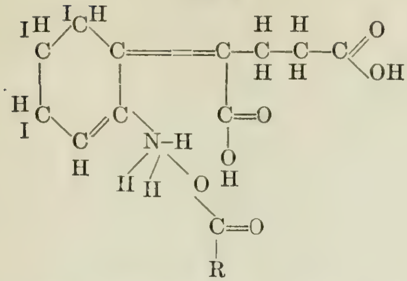

Fig. 6.—The formula for an organic salt of the amino group in the open-ring structure of thyroxin.

All the chemical reactions of thyroxin center around the nitrogen group; and the specific reactions which thyroxin brings about are due to the unique configuration of the molecule, which imparts to the nitrogen group its special powers.

After the exact chemical nature of thyroxin had been determined, it became of great interest to find the relation between thyroxin and the normal thyroid secretion. In brief, it may be said that the clinical department in this clinic is convinced from experience based on the administration of more than 100,000 doses of thyroxin to several hundred patients, that the entire physiologic activity of desiccated thyroid is contained in the single chemically pure substance, thyroxin. There is nothing which desiccated thyroid can do in the relief of cretinism and myxœdema which thyroxin cannot do.

From a group of about thirty high-grade typical cases of myxœdema, two have been chosen to illustrate its activity.

Case I.—A girl, aged twenty, had suffered from a hypothyroidism for seven years. The patient was in a high-grade myxœdematous condition with considerable œdema and all the other well-known and classic signs and symptoms. She was given 1.6 mg. of thyroxin daily. At the end of eighteen days she showed definite signs of excessive thyroid medication. She had lost ten pounds; her pulse was 120. In Figures 7, 8, 9 and 10 the relief in the œdema is shown. The striking feature about this case is the very small amount of thyroxin required to initiate the improve-

ment and entirely relieve the condition (Figures 7, 8, 9 and 10).

Case II.—A woman, aged forty-seven, came to the clinic chiefly because of mental symptoms. This patient had become slowly incapacitated during the last ten years, until at the time of examination she had ceased practically all activities. She required a trained nurse, at times was irrational, and had spent about six months in a sanitarium, with a diagnosis of dementia præcox and a hopeless prognosis.

We administered large amounts of thyroxin for three weeks, and the patient was entirely relieved; the œdema and subjective symptoms had disappeared, and she was bright and alert. She returned home to take up her household management, and since that time has been practically normal.

Although the mental condition of this patient was her reason for coming to the clinic and was perhaps her most striking abnormality, still the administration of thyroxin produced a change throughout the entire body. She is now taking approximately 8 mg. of thyroxin each week. More or less than this amount produces subjective symptoms. A correct diagnosis had not been made elsewhere, because desiccated thyroid had been given and produced no improvement in the symptoms. This may be explained by the fact that a large amount was necessary in order to initiate the improvement. Very large doses of thyroxin were required during the first few days, but after the first response the patient became as sensitive to thyroid medication as the normal person. The unusual resistance probably was due to the patient's non-absorption of the material from the alimentary tract. After the improvement had been brought about, the rate of absorption increased, and the patient reacted in a normal manner (Figs. 11, 12, 13, 14 and 15).

Thyroxin not only relieves the symptoms of myxœdema, but also influences growth in a manner similar to desiccated thyroid.

Case III.—A girl, aged ten, came to the clinic suffering from thyroid deficiency. The child had not received desiccated thyroid at any time. She was brought for examination because of her stunted growth; she was thirty-seven inches high and weighed thirty-seven pounds (Figs. 16 and 17). During three months

Fig. 13.

Fig. 14.

Fig. 15.

Fig. 13 (146434).—Appearance of patient upon entering the clinic.
Fig. 14. (146434).—After twenty-four days' treatment, during which time the patient received thyroxin.
Fig. 15. (146434). The patient almost five years later, during which time she had continuously taken 8 mg. of thyroxin every week.

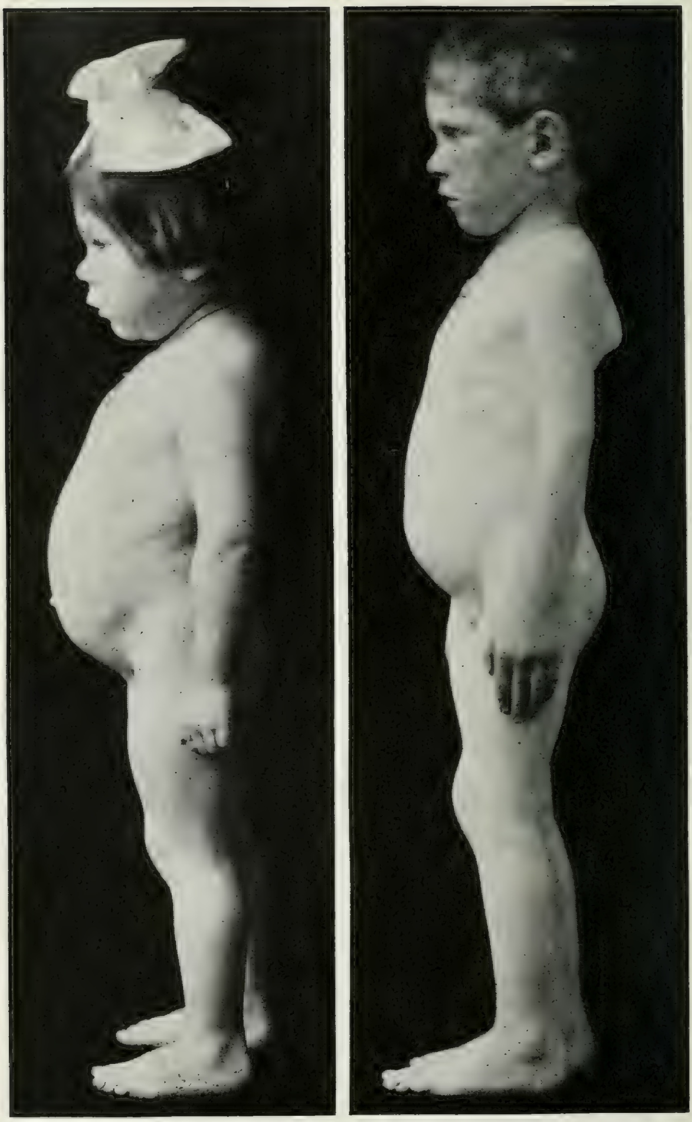

Fig. 16 (118156).—At the time thyroxin treatment was begun and six months later. Increase in height, four inches.

Fig. 17 (118156).—At the time thyroxin treatment was begun and one year later. Increase in height, six inches.

she was given all the constituents of the thyroid other than thyroxin. This produced no visible effect. She did not grow taller, and there was but slight change in her skin and general appearance. She was then given 0.4 mg. of thyroxin every day for six months, during which time she grew four inches. She has continued to take thyroxin in doses varying from 0.4 to 0.8 mg. up to the present time. A table of her heights and weights is as follows:

Date	Weight Pounds	Height Inches
January 4, 1915	37	37
January 27, 1915	35⅓	38
February 27, 1915	36¾	38
April 2, 1915	38	39
May 5, 1915	37	39
June 4, 1915	37½	39¾
July 8, 1915	39	41
August 5, 1915	41½	41½
September 4, 1915	41½	41¾
October 16, 1915	42¾	41¾
November 13, 1915	45	42
December 14, 1915	44¾	42¼
January 16, 1916	45½	43
February 15, 1916	44	43¼
March 17, 1916	45½	43¾
April ?, 1916	43	43¾
May ?, 1916	46	44
June 18, 1916	47	44⅛
July 14, 1916	46½	44½
August 16, 1916	47½	45¼
September 17, 1916	48½	45½
October 22, 1916	50	45½
November 17, 1916	50½	45¾
December 6, 1916	50½	45⅝
January 16, 1917	52	46
March 13, 1917	52	46½
April 19, 1917	53	46¾
May 25, 1917	54	46¾
June 19, 1917	53	47
July 23, 1917	53	47
August 22, 1917	53	47¼
September 25, 1917	54	47¾
October 29, 1917	56	47¾

Date	Weight Pound	Height Inches
November 27, 1917	57	48
December 20, 1917	56	48⅓
January 16, 1918	57	48⅓
February ?, 1918	58	48⅓
March 30, 1918	58½	48⅓
April 20, 1918	59	48⅓
May 30, 1918	58½	48½
June 26, 1918	58	48½
July 21, 1918	57½	48½
August 30, 1918	58	48½
September 24, 1918	57	48¾
October 28, 1918	58	49
November 30, 1918	58½	49½
December 31, 1918	58	49¾
January 31, 1919	59½	50¼
February 27, 1919	60	50¼
March 23, 1919	62	50¼
April 27, 1919	60	50½
June 22, 1919	59½	50½
July 21, 1919	60	52
August 29, 1919	65	52½
October 20, 1919	64	52½
November 30, 1919	67	53
January 1, 1920	68	53¾
February 13, 1920	68½	54
April 3, 1920	70	54
Increase in weight	89 per cent.	
Increase in height	46 per cent.	

To-day this child is bright and active; she attends school and is restored as nearly to normal as is possible, considering the late time in her life the thyroid deficiency was recognized. She has received no medication but thyroxin, and all the improvement is due to this single substance. The patient not only grew taller, but also her skin became soft and moist, and her hair, which was coarse and thin, became thicker, softer and much longer. Her mentality is wonderfully improved.

This patient is a typical example of the manner in which thyroxin affects the animal organism. No cell in the entire body remained unchanged. Every cell was stimulated to greater activity. In this connection it is also to be noted that the patient

was not given excessive amounts of thyroxin. An overdosage of the substance produces effects that are almost as deleterious as an absence of thyroxin.

The thyroid is so deeply involved in life processes that it cannot be treated as a separate entity, and its activity can be recognized only by the results of its absence or superabundance, and so its influence has been known up to the present time, not in terms of an active process, but only as clinical entities. The result of this viewpoint in the past has been to relate the function of the thyroid to restricted portions of the body, such as to the nerves and the growth of bones, and to lead away from the consideration of the thyroid as an influence exerted throughout the body and presiding over the control of the rate of chemical reactions which are carried out by all cells, and are essential to life itself. Although clinical diagnosis, surgery and pathology have been the avenues of approach to our knowledge of the function of the thyroid up to the present the ultimate proof of any hypothesis cannot be secured by these methods of investigation. They must, of necessity, stop short of the ultimate proof, since they deal not with a study of the chemical reactions involved, but with the end results of the reaction.

A knowledge of the chemical groups present in thyroxin enables us to understand better what chemical reactions are possible with the substance. In all its chemical reactions thyroxin exhibits either acid or alkaline properties, and it is through its acid and alkaline groups that thyroxin manifests its physiologic activity. This may very readily be demonstrated by merely replacing one hydrogen group of thyroxin by a larger molecule. This slight alteration renders the entire molecule physiolgically inert.

Although thyroxin profoundly affects the rate of physiologic processes, there is nothing which thyroxin can do in a chemical sense which cannot be done by other substances. The one difference lies in the fact that thyroxin is not destroyed when it functions and can be used as a catalytic agent times without number, whereas other chemical substances with the same chemical groups are more readily destroyed and do not act as catalytic agents.

A fundamental relationship must exist between the chemical configuration of thyroxin and the physiologic reactions brought about by its presence in the body.

In the myxœdematous patient the thyroid is either entirely absent or it has ceased to function; and it has been found that in all patients with high-grade myxœdema the energy output during rest and at least twelve hours after eating approaches a uniform level which is 40 per cent. below normal. Why all high-grade myxœdematous patients approach the same level is unknown. One explanation is that in the absence of thyroxin its function is taken up by other compounds and life is maintained, but at a lower level. According to this view, the addition of the thyroid to the animal organism permits of greater fluctuations in energy output, and it is the mechanism by which a normal energy output is maintained, irrespective of the environment. By varying the amounts of thyroxin present in the tissues the rate at which energy is produced may be varied, other factors remaining constant. It, therefore, became of interest to determine the amount of thyroxin which normally is present in the tissues and the blood. The amount in the gland has already been determined. It probably is in the neighborhood of from 7 to 8 mg. By a recent improvement in the method for the determination of iodine, it has been possible to show that the iodine content of normal blood is about one and one-half parts in ten million. The iodine content of tissues is about two and one-half parts in ten million and the iodine content of the liver is between three and four parts in ten million. This is the total amount of iodine present. What percentage of this is in the form of thyroxin is not known. Granting, however, that 100 per cent. of the iodine is in the form of thyroxin, these figures represent a maximum beyond which thyroxin cannot be present. It means that the entire blood stream of an adult contains not more than 2 mg. of thyroxin, and that the amount in the entire body is not more than 25 mg. or less than one-half of one grain.

With regard to the relation between the thyroid gland and normal physiology, investigators, each in turn, have claimed that the gland presides over practically every possible function of the

body. Its relation to the nervous system, the circulation, the other glands of internal secretion, notably the sex glands, its effect upon immunization and the production of immune bodies, its relation to growth and old age are problems which may be merely mentioned. Recently the effect of the thyroid on the basal metabolic rate has been more and more investigated; and the far-reaching results of the studies of Lusk, Benedict, DuBois, Boothby and Peabody on the basal metabolic rate show that in this study probably lies the clue to a more exact knowledge of thyroid activity and the explanation of the chemical reactions involved. It was a matter of considerable interest, therefore, when Plummer, at our Clinic, showed that a quantitative relationship exists between thyroxin and the basal metabolic rate. The administration of 1 mg. of thyroxin to an adult weighing approximately 150 pounds increases the basal metabolic rate 2 per cent. The administration of 2 mg. increases it 4 per cent., the administration of 10 mg., 20 per cent. This quantitative relationship is of great aid in understanding the activity of the gland in normal and pathologic conditions. It places a quantitative value upon a gland that has of necessity in the past been studied merely from clinical observations, subjective and objective signs and symptoms. The administration of thyroxin produces nervous manifestations, palpitation of the heart, loss of weight, and so forth; but when the metabolic rates of various persons are determined, it is soon apparent that interpretation of the action of thyroxin when based on the clinical changes, pulse rate and nervous symptoms, and when based on the actual increase in energy output, as shown by the quantitative determination, may be widely varying. Myxœdematous patients at our Clinic are now treated in a quantitative manner. If the metabolic rate is 40 per cent. below normal they are brought to normal by the administration of 20 mg. of thyroxin. They are then maintained in a normal condition by the proper dosage of thyroxin given daily.

The effect of administering thyroxin was pointed out as early as 1914 in some experiments on dogs.[9] At that time it was found that there is a marked delay in the production of symptoms. As

many as thirty-six or forty-eight hours, and sometimes more, were necessary before a marked response to an injection of thyroxin was obtained. Furthermore, it was found that after a single administration the effect was very slight or entirely absent, but that typical hyperthyroid symptoms could be produced by successive daily injections. The explanation of the delayed action is not entirely clear. Undoubtedly, many factors are involved, but two will be mentioned at this time:

First is the fact that there is a limit to the amount of thyroxin which the tissues will absorb from the blood stream. Normally the tissues contain more iodine than does the blood. One week after the injection of thyroxin in a cat it was found that the blood, after ether anæsthesia, contained ten times more iodine than the tissues when based on a comparison of 100 gm. each. Not only do the tissues refuse to take up the injected thyroxin, but there seems to be a limit to their capacity for the absorption of the compound. If thyroxin is given in a single large dose, it is excreted in the bile, and its immediate effect is not at all apparent. The establishment of the fact that the tissues will take up thyroxin only to a limited extent suggests that in the normal condition there must be some regulating mechanism which maintains an equilibrium in the thyroxin distribution during times of rest and of activity.

The second factor explaining the delayed action after the injection of thyroxin is the fact that the mere presence of thyroxin in the tissues does not of itself mean an increased energy output. Forty minutes after an intravenous injection the iodine content of a cat's muscle was twenty times the normal, and yet the energy output was not at that time increased above normal. Many hours are required to build up a response within the animal organism as a whole before the full effect of thyroxin can be manifest. Whether the other ductless glands have to be stimulated or some agents within the tissues themselves have to be elaborated is not known. Plummer has shown, however, that with each of a series of thirty-five myxœdematous patients the maximum effect was not reached until the tenth day. The increased basal metabolic rate was maintained for many days after this and did not reach its

former level until about three weeks after a single injection of thyroxin. Whether precisely the same time relations hold true in a normal person is not known. The fact that there is a quantitative relationship between the amount given and the metabolic rate which persists for more than three weeks is the strongest evidence that thyroxin acts as a catalytic agent.

If the chemical reactions which permit thyroxin to influence so profoundly, the basal metabolic rate are considered, it is apparent that in thyroxin there is the possibility of localizing the active groups by changing the configuration of the molecule by methods well known in organic chemistry. It is possible to replace iodine with bromine, chlorine or other groups. It is possible to vary the structure of the molecule in other ways, but the first essential is to determine whether it is the organic nucleus or the iodine within the molecule which is responsible for the physiologic activity of the compound. As soon as iodine was discovered as a normal constituent of the gland, and before the nucleus to which the iodine is attached had been established, clinicians and experimental investigators were concerned with the relation between iodine and thyroid activity. Now that the nucleus to which the iodine is attached is known, the problem is broadened, and we must consider whether it is the iodine or the nucleus which is really responsible for the physiologic activity of the molecule. By replacing the hydrogen of the imino group with a larger molecule the effect on the metabolic rate is destroyed. The iodine by this alteration is not affected, and apparently it could function the same in both substances. The fact remains that the acetyl derivative is without effect on the metabolic rate. Thus there is doubt thrown on the hypothesis that iodine is the essential portion of the molecule for the physiologic activity of thyroxin.

The proof of the chemical reactions involved when thyroxin functions will ultimately be available by working through the synthetic preparation of thyroxin and compounds closely related, but it is possible to prove that the effect of thyroxin in the relief of myxœdema and the effect of thyroxin in producing certain other physiologic reactions may be due to different portions of the molecule of this single substance. Gundernatsch, Morse,

Allen, Uhlenhuth, Swingle and many others have been investigating the effect of thyroid substance, iodine, and other compounds on the rate of the metamorphosis of the tadpole to the frog. Gundernatsch first showed that the feeding of desiccated thyroid to tadpoles increases in an extraordinary manner the speed with which they became frogs. The usual time of metamorphosis is from two months to two years, varying with the species, but the administration of thyroid cuts this down to as short a time as from five to eight days.

When thyroxin was given to tadpoles, it was found that extremely small amounts bring about the metamorphosis of the giant tadpole in a very striking manner. If more than 0.01 mg. is administered intraperitoneally, metamorphosis is brought about, but the tadpole dies after eight or ten days. If less than 0.01 mg. is given intraperitoneally the metamorphosis is brought about, and the frog sometimes lives. This has also been tried on smaller tadpoles, but the amount required to bring about the change is smaller than can be determined my any method so far devised. The administration of the acetyl derivative of thyroxin to a myxœdematous patient does not improve the condition of the patient. There is no visible effect. No toxic symptoms can be produced in animals or in man by the administration of the acetyl derivative. It seemed possible, therefore, to determine by the administration of the acetyl derivative to tadpoles whether it is the nucleus which is essential for physiologic activity or the iodine. This was done, and it was found that the acetyl derivative brings about the metamorphosis of the tadpole, not quite as effectively as thyroxin but in a very striking manner. The activity of thyroxin, therefore, appears to be divided into two distinctly different reactions. One is its effect on the basal metabolic rate or, in other words, the energy output. This is a catalytic action, is carried out over a period of more than three weeks from a single dose, and is vitally related to the chemical processes involved in the production of energy. The other is the physiologic reaction which results in the metamorphosis and differentiation of the organism from a larva to the adult stage, as typified in the metamorphosis of the tadpole. This action is little understood,

but since iodine derived from many different compounds produces the same action, it seems probable that some specific type of combination of iodine is the active agent in this action, although other substances may act the same. It has been shown that iodine splits out from the thyroxin molecule in the form of hypoiodous acid and not as free iodine. This finding has a direct bearing on the relation between iodine and the metamorphosis of the tadpole, but it will not be discussed at this time. How closely these two different reactions brought about by thyroxin will ultimately be proved to approach each other is not now apparent, but that they are due to two distinctly different chemical processes appears probable from the preliminary results already obtained.

An understanding of the chemical nature of thyroxin is of the greatest aid with regard to the relation between thyroxin and pathologic conditions found in thyroid disturbances. The ability to produce a definite clinical syndrome identical with the condition found in toxic adenoma by the injection of a single crystalline substance throws a great deal of light on this condition. Persons with hyperthyroidism may be divided clinically into two definite groups: Those with frank exophthalmic goitre with exophthalmos and the classical symptoms usually described as Graves' disease, and those with so-called non-exophthalmic goitre, produced by a toxic adenoma, a condition which has been pointed out by Plummer. Clinically there are many differences between the two groups. No doubt there are chemical differences in the causes of the symptoms. The administration of thyroxin produces the symptoms of toxic adenoma, but in no case, either in experimental animals or in man, has exophthalmos or the entire picture of exophthalmic goitre been produced by the administration of thyroxin. If a normal person is given thyroxin until toxic symptoms develop and the administration is then suddenly stopped, the recovery is entirely similar to the recovery of patients who have had a toxic adenoma removed surgically. The time curve of the drop in the metabolic rate with a prompt return to normal is quite striking in every case. The basal metabolic rate curve in relation to time after operation for exophthalmic goitre

is not the same. It seems probable, therefore, that in toxic adenoma the cause for the high metabolic rate, the nervous symptoms and loss of weight is due to excessive production of thyroxin within the body, and that in exophthalmic goitre some other chemical substance or substances, possibly very closely related to thyroxin, is the cause. Speculation is of but little value. The important fact is that the investigation of this distressing disease is now possible through the field of synthetic organic chemistry, and new avenues of approach are opened up for the study of the etiology and relief of this condition.

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DISEASE is the accomplice of war. To the uninitiated, at first glance, it seems that the chief wastage of man power in armies is produced by weapons of the enemy; to the initiated, on the other hand, it is well known that the wounds produced by bacteria are as fruitful a source of disability as those caused by bullets. One reason for this attitude on the part of the casual observer is that the injuries of battle are more spectacular than those of disease. They are more unusual, both in their mode of production and in the manner in which they respond to treatment. The care of the wounded often yields striking results. The humanitarian instincts, aroused by the fact that the injuries were received as a direct result of sacrifice, properly lead to the building up of an intricate organization for the care of the wounded. The problems must be largely solved in the actual presence of war. Sickness, on the other hand, is more easily tolerated, because it is the lot of most men to suffer illness. The problems of disease are always with us; most of those presented by war have been studied in times of peace. Almost in direct proportion to the rate at which a given disease causes fatalities, in contradistinction to casualties, are effective prophylactic measures studied and put into effect. The antivenereal disease campaign in our own army is a striking exception to this statement. The prophylaxis of typhoid fever and small-pox was more effective than that of dysentery or the pyodermias. It may be urged that the measures for preventing the first two diseases are more easily applied in war. This is true; but had the prevalence of the fatal disease, typhus fever, been as great as that of the non-fatal, but disabling affection, trench fever, no doubt more effective measures would have been early instituted for combating it.

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The complete ignorance of the existence of such a disease as trench fever, with the consequent lack of knowledge as to its mode of spread, made it impossible to apply prophylactic measures until this information was available. A very real impediment to the study of a disease during war is that the patients are rarely under the same observer or group of observers during the entire course of their illness. This was especially true during the first part of the recent war, before the lines had become stabilized and hospitals stationed close enough to the front to permit the retaining of the sick for longer periods.

For these reasons it was not generally recognized until the spring of 1915 that a hitherto unknown disease was fairly widespread throughout the combatant troops. At this time, medical officers in both the British and the German armies almost simultaneously noticed a five- or six-day relapsing fever in many patients, who complained of severe and persistent pains in the shins. Graham,[1] Herringham [2] and others saw many examples of this condition among British troops from the trenches but not among the troops in the rear; so the name of trench fever was applied. His [3] and Werner [4] saw their first cases on the east German front in Poland and Wolhynia. The former applied the name Wolhynian Fever to the disease because of the supposed source of the infection; the latter used the term five-day fever because of the interval between relapses. Because of the almost simultaneous appearance of cases on the two fronts, it is difficult to determine the original source of the infection; but Grätzer,[5] a battalion medical officer in the 84th Austrian Infantry Regiment, states that he had observed cases among soldiers under his care since the winter of 1914. He gave a very good description of the malady; and because of its increase in winter and when crowding of the soldiers was necessary, attributed the spread to some insect vector. He saw his first cases when his regiment was on the Nida, and learned from the inhabitants of that region that a similar condition was known to them before the war. Franke [6] also states that he recognized the disease as having occurred in Lamburg in previous years, when it was known as influenza with relapses. It seems, therefore, from the evidence at hand, that

the original source of the infection was somewhere in Russia and that the disease was spread to all of the battle fronts in Europe by German and Austrian troops as they moved from one area to another.

It was early noted by some observers that an enlarged, hard spleen often accompanied by perisplenic tenderness could be demonstrated in many of the patients. The outstanding features of typical cases were, however, the sudden onset with marked febrile reactions, headache and general body pains, closely resembling the onset of influenza, but followed in a few days by pain and tenderness of the shins and a spiky type of relapsing fever. There were many patients who complained of painful shins, especially at night, but in whom there was no history of an abrupt onset, or of a distinct febrile bout. Various explanations, such as long marches, flat feet, standing in mud and water, rheumatism or myalgia were suggested to account for these unusual pictures. In still other patients with similar symptoms, the pyrexia was continuous, resembling that of typhoid or paratyphoid fever, or intermittent, like that of sepsis.

Much confusion in diagnosis arose from the presence of so many patients having certain symptoms in common, yet presenting, on the other hand, so many individual variations. In fact, it was so difficult to establish a normal or typical picture of the disease that the terms P.U.O. (pyrexia of undetermined origin) or influenza were applied in many instances.

The ignorance of the existence of atypical forms of trench fever, the practical impossibility in many cases of making a positive diagnosis and the great difficulty of establishing adequate sanitary measures during war of movement, were all factors that resulted in the infection being widespread before the disease had become recognized as a separate entity. A serious study to determine its nature was soon undertaken by investigators on both sides of the line. The first extensive report was that of McNee, Brunt and Renshaw,[7] who used as experimental subjects British soldiers who had volunteered for inoculation. These workers showed that the virus of the disease was contained in the whole blood and that it could be transferred from man to man by intra-

venous or intramuscular injection. In their experiments the plasma or serum obtained from infectious blood did not contain active virus unless hæmoglobin tinged. The red blood cells, on the other hand, were infectious, even after five washings. Material known to contain virus was not infectious after passage through a Berkefeld filter; but in spite of this fact these workers were unable to demonstrate microscopically any microörganism. This work was unfortunately interrupted before it was shown conclusively that trench fever was not a modified form of typhoid or paratyphoid fever, and before it had been established that the infection was transmitted by some insect vector. In spite of the questions that were left undecided, the observations of McNee, Brunt and Renshaw stand as the first important contribution to the nature of this disease. They showed that the inoculation of blood from a patient with the short form of fever might result in infection showing a prolonged course, with spiky relapses every fifth day; the essential unity of a disease with multiform manifestations was therefore established.

In the year following this work there were many unconfirmed reports from German workers that they had been able to transmit the infection to animals. Jungmann and Kuczynski [8] claimed to have produced a fatal infection in mice, and Strisower [9] reported that both cats and mice succumbed to a fatal infection following inoculation with blood from trench-fever patients. The animals did not present a clinical picture similar to the disease in man; nor were they successfully inoculated through several generations. Most workers agree, however, that it is impossible to transmit the typical disease to the ordinary laboratory animals, although extensive experiments have not been attempted with the higher apes. For this reason all experimenters have found it necessary to resort to the inoculation of human volunteers in order to obtain any definite, useful information in reference to the nature and mode of transmission of the infection. Werner and Benzler [10] successfully inoculated themselves by means of intramuscular injections of blood from trench-fever patients. Six months later Werner allowed himself to be bitten by lice that had previously fed upon trench-fever patients, and after an incubation period of

eight weeks developed a mild illness that was diagnosed as Wolhynian fever. Kuczynski [11] also contracted the disease after being bitten by supposedly infected lice. In all of the experiments carried on by the German workers there is no mention that the inoculated subjects had been isolated from other cases of trench fever, or that special efforts were made to eliminate other sources of infection. It is a well-known fact that doctors, nurses and attendants in military hospitals wherever the disease was prevalent were especially subject to accidental infection. Furthermore, there is little evidence to show that the stocks of lice were free from infection before use in the experiments. Davies and Weldon,[12] of the English army, allowed themselves to be bitten by lice immediately after an infecting feed on trench-fever patients; the lice were originally collected from soldiers. One of them developed trench fever twelve days later. The same criticism that has just been made of the German work can be equally well applied to their experiment. It is not intended to underestimate the efforts of any of these workers, but rather to point out that the results were not sufficiently conclusive to warrant the undertaking of extensive prophylactic measures along any particular line.

Late in 1917 Pappenheimer and Mueller,[13] of the Presbyterian Base Hospital of New York, succeeded in transmitting the disease to one of three volunteers by allowing lice to feed first upon several trench-fever patients and then upon the volunteers. In their experiments the volunteers were kept carefully isolated. Unfortunately, the patient to whom the disease was transmitted suffered from a complicating femoral phlebitis. I saw him on several occasions and have little doubt that he had true trench fever. Here again it could not be positively asserted that the lice were not infected before they fed on the trench-fever patients.

These isolated observations were all highly suggestive, but awaited confirmation by more extensive experiments before they could be translated into active effort. In fact, there were negative experiments, such as those recorded by Sundell and Nankivell,[14] and many reports of patients who denied having been bitten by lice that threw doubt upon the louse-transmission hypothesis.

Epidemiological studies were highly unsatisfactory because of the constantly changing population in most military units. The proof that rats were the active agents in the transmission of spirochætal jaundice naturally suggested that trench fever might be spread in a similar manner. It is evident that it was impossible to frame any effective program to combat the spread of the disease in the face of so much conflicting evidence and opinion.

In the meantime, accumulated evidence showed that trench fever was one of the largest sources of wastage of man power in the fighting armies. It is estimated that during the years 1917 and 1918, before the influenza epidemic, it was the cause of from one-fifth to one-third of all of the cases of illness in the British armies in France. The German reports indicate that this disease was responsible for at least one-fifth of the illness in the armies of the Central Powers. Although the illness was never fatal, it resulted in prolonged disability. A report from the Boulogne Base [15] of the British army shows that patients with trench fever were unfit for military duty for an average of from sixty to seventy days, and that in addition at least 10 per cent. of them became semipermanent invalids.

This is a brief sketch of the state of our knowledge at the time of the formation of two commissions to study the disease more carefully. It was perfectly evident that to obtain the most accurate information it was necessary that the experimenters should be free from the manifold duties of an army medical officer. The conditions under which members of these commissions worked satisfied these requirements. The British Commission in London had the advantage of permanent hospital and laboratories and the assistance of the workers of the Lister Institute. Volunteers for inoculation and fresh cases of the disease were not so available as in France. It was possible to conduct the experiments in a more leisurely manner and thus to study in more detail the problems as they arose.

The Commission * formed under the auspices of the American

* The Commission consisted of Majors Strong and Opie, Captains MacNeal, Baetjer and Pappenheimer, Lieutenant Rapport and myself, all of the Medical Corps of the United States Army, and Captain Peacock, an entomologist from the Royal Army Medical Corps.

Red Cross, on the other hand, started its work under field conditions. Later it was necessary to move the laboratory, patients and personnel to Paris, where better facilities were available. We were compelled to answer the problems as quickly as possible. We had the advantage of starting the work in a place where numerous examples of fresh infection of the disease were available and where the Trench Fever Commission of the British Expeditionary Force had been carrying on clinical studies for some time. The advice of experienced observers was, therefore, available both in the selection of suitable patients from which to obtain the virus and in the decisions as to the nature of the disease produced. Every facility at their disposal was offered by both the British and American military and medical authorities. The members of the commission were chosen because they could carry out their particular part of the work with the least possible delay. Captain Peacock was loaned by the R. A. M. C. to help in the entomological work because of his previous experience with the life and habits of insects.

These details are related in order to make clear the conditions under which the answers to the various problems were obtained. Throughout the entire period of our work there was the closest coöperation between all of the interested organizations. As fast as positive results were obtained by one commission they were made known to the other, and thus much time was saved to both. It is only natural that different lines of investigation should have been followed by different workers and somewhat divergent results obtained; but in the main facts the two commissions agree. This communication, therefore, will consist largely of a résumé of the work of these two bodies.

Before proceeding, however, it is well to credit the volunteers for the large part they played in the success of the experiments. Probably in the investigation of no other disease have so many men submitted themselves to artificial inoculation. Even though they could be reasonably sure that their illness would not be fatal, they knew that they would suffer much pain and incapacity for an indefinite period. In spite of this knowledge, both our own soldier volunteers and the British civilians who offered them-

selves underwent the trying experience with the greatest fortitude. As a direct result of their sacrifice, much information was obtained that led to the institution of measures for the prevention of the spread of trench fever in both military and civilian population.

It will be recalled that although McNee, Brunt and Renshaw had fairly well proven, by human transmission experiments, that trench fever was a disease entity related in no way to the typhoid-fever group, there were many clinicians who still held that the malady was a form of enteric fever modified by the immunity that had been induced in soldiers by protective inoculations. There were many cases in the British enteric-fever hospitals diagnosed by means of agglutination reactions as typhoid or paratyphoid fever that presented clinical pictures resembling trench fever in almost every respect. One of our first problems was, therefore, to confirm McNee's observations and to establish definitely that the patients with whom we were working were not suffering from any other disease than trench fever. Over thirty volunteers [17] were inoculated with blood or some fraction of blood. In all of the original patients from whom the virus was obtained, as well as in those that developed the disease as a result of inoculation, it was proven by bacteriological examination that no known bacterium played any etiologic rôle in the condition under consideration. Like McNee and his co-workers, we found that the whole blood contained the virus, but in contradistinction to their findings, we determined that the plasma, obtained from citrated blood, was always infectious. In four out of five experiments the incubation period in the patient inoculated with citrated plasma was shorter than in control patients inoculated with the whole blood. It seemed, therefore, that the plasma contained the virus in greater concentration. Clear serum, obtained by centrifugalizing coagulated blood, no longer contained active virus. A similar result with serum was recorded by the British Commission.[18] It seems, therefore, that the virus is either enmeshed in the fibrin network of the blood clot or is destroyed by some substance set free during clotting. The incubation period in patients inoculated with citrated blood after standing outside of

the body for two or three hours was longer than in those patients that were inoculated immediately.

In connection with the problem of immunity in trench fever it is interesting to note that the injection of blood obtained from patients on the first to the fourth days of the disease resulted in positive infections with an incubation period of from five to seven days; while in those that were inoculated with blood obtained on the sixth or seventh day the incubation period was thirteen to twenty days. Furthermore, a susceptible subject injected with blood from a patient during an active relapse on the eighty-second day did not contract trench fever. Later experiments make it reasonably certain that this blood contained virus. This evidence points to the development of immune bodies in the serum of patients as the disease progresses; such immunity explains to a certain extent the mechanism of recovery.

Our attempts to pass the virus in the plasma through a Berkefeld filter met with failure, as did the filtration experiments of McNee and his co-workers. One patient inoculated with the filtrate of crushed and ground infectious erythrocytes, developed symptoms and signs of the disease from the eighth to the eleventh day, but no fever until the fiftieth day after inoculation. While the results in this single experiment were suggestive, more conclusive evidence of the filterability of the virus was not forthcoming until later, and hence will not be discussed until other evidence of the nature of the infectious agent is presented.

In none of our experiments was the virus demonstrable in the fæces of trench-fever patients; on the other hand, it was occasionally present in the mixed sputum and saliva. In contrast with these findings, the frequency with which the urine of trench-fever patients was infectious was noteworthy. All of five subjects inoculated with unfiltered urine sediment developed the disease, although one patient was inoculated three times before positive results were obtained. The material for inoculation was prepared by contrifugalizing urine, drying the sediment to a gummy mass and keeping it at room temperature. The combined sediment collected on different days from several patients was used in all of the experiments. Here again the inoculation was effected

by applying the material to lightly scarified skin. This series of experiments demonstrated somewhat the resistant nature of the virus in that the high salt concentration that resulted from evaporation of urine was sufficient to kill most bacteria and spirochæta. There is, however, some evidence that this manipulation did decrease the virulence of the infectious material, for in four out of five patients inoculated with urine sediment the incubation period was two weeks or more. Another explanation for this longer incubation period is that the virus may have been present in the urine in not so high concentration as in the blood. In framing measures for the prevention of trench fever, these experiments indicate the necessity of considering the urine and sputum as possible if not the chief sources of infection.

While the foregoing experiments were an important part of our work in that they proved beyond doubt the essential nature of trench fever and provided known sources of infection for the elucidation of other problems they were only contributory to the main object of our commission—namely, the determination of the rôle of insects in the transmission of the disease. From the beginning it was evident that military operations might interfere with the continuation of the work. The experiments were, therefore, planned to give a positive answer in the shortest time.

All of the lice used were reared from eggs and fed upon normal subjects. Altogether, eleven different people served to feed these normal lice, without developing the disease. Similar findings of the British Commission should serve to quiet the contention that the symptoms of trench fever may be produced by the action of normal lice.

In order to infect the lice they were allowed to feed upon trench-fever patients by means of the box method. Between feedings they were kept at about 30° C. in entomological boxes prepared from ordinary cardboard pill boxes and were fed two or three times a day by placing the open side of the box upon the arm of the subject for thirty minutes. After several infecting feeds, they were transferred to especially prepared cells and placed upon the normal subject. These cells were designed so that the lice might live under as normal conditions as it was pos-

sible to reproduce artificially. A piece of flannel shirting was placed inside of a larger piece of calico, which was then fastened to the arm of the subject by means of adhesive tape; the arm was finally covered with cotton and enclosed in a sleeve that was fastened to the skin at the top and bottom. In this form of container the insects could feed, breed, live and die in almost the same manner as when they infest the clothing of soldiers. The only limitation of their normal activities was that they could not migrate to other portions of the body or to other persons. It was difficult for the volunteer to scratch the skin through the several thicknesses of cloth and cotton, so that at times when the cell was removed for inspection he was allowed or encouraged to scratch. In some instances, however, there were no lesions of the skin other than those produced by the stabbers of the lice. Among twenty-three subjects who harbored infectious lice in this manner, eighteen, or 78 per cent., developed trench fever. Two others, in whom an especial effort was made to prevent any skin lesion except that resulting from the bite of the lice, also developed the disease after an incubation period of four and five weeks respectively. In these two experiments the lice never came into direct contact with the skin of the subject, but were allowed to feed by biting through the meshes of the chiffon cover of the box in which they were kept; in the intervals between feeds the boxes of lice were put in the incubator. In the large majority of our experiments, therefore, infectious lice living under natural or artificial conditions were able to transmit the disease to susceptible subjects. In some instances the lice were on the subject for as short a time as three days; in others for as long as thirty days. In some experiments, after the infecting feeds, the lice were transferred to successive subjects in order to eliminate possible mechanical transference of the virus. The incubation periods varied between fourteen and thirty-eight days, with an average of about twenty-one days. This long incubation period should be kept in mind in connection with the scarification experiments discussed later.

The British Commission [18] was less successful in transmitting the infection by the bites of infected lice. In a total of eight

experiments only two subjects developed the disease. In all of these trials, however, the lice were fed entirely by the box method, as in two of our experiments mentioned above. The difference in the method employed by the two commissions explains, no doubt, the difference in their results. The failure of the workers in London to transmit the disease by the bites alone of infected lice led them to study the effect of applying the excreta of such lice to scarified skin. This resulted in positive infections in the large majority of their experiments. This fortunate outcome opened up a fruitful field which was explored by them with brilliant results. In demonstrating this form of inoculation they developed a method that permitted the study of the evolution of the virus in both lice and patients.

It was shown that the excrement of practically all lice that have bitten trench-fever patients is infectious when applied in suitable quantities to the skin of normal individuals, either by scarification or subcutaneous injection. Volunteers could also be infected by introducing the material into the conjunctival sac but not by insufflation into the nose or by ingestion with the food. The incubation period in the majority of the patients infected by cutaneous scarification was from seven to nine days; that from conjunctival inoculation was about twice as long.

It was established that a certain interval must elapse between the infecting feed and the excretion of actual virus by the lice. In one series of experiments when the insects were fed upon a patient with trench fever on the second day of his disease, this interval was five days; in another, when the infecting feed was from a patient on the seventy-ninth day the interval was twelve days. An observation of even as great interest was the length of the incubation period in the volunteers infected with excreta passed by lice on different days after the infecting feed. For instance, the incubation period in the patients infected with excrement passed on the fifth and seventh days after the infecting meal was sixteen and thirteen days respectively; while in the patients infected with excrement passed from the ninth to the twelfth days, it was seven to nine days. This evidence points to one of two hypotheses: Either the virus of trench fever goes

through a developmental cycle in the body of the louse, or it is taken into the body of the insects in extremely minute quantities, and there must undergo an increase before it can be excreted in sufficient quantities to infect man. The fact that within certain limits the incubation period is shortened by increasing the amount of virus most easily explains why the first virus passed by the lice is less actively infectious than that passed after the ninth day. The minute quantity of the virus that may induce an attack of the disease is shown by the fact that 0.1 of a milligram of excrement injected subcutaneously was infectious, while 0.05 of a milligram was not. The proof that after a lot of lice have been infected they continue to pass the virus during the remainder of their life also supports the hypothesis that the virus simply increases in the body of the parasites. It was further demonstrated that a single louse may pass active virus as late as thirty-two days after it has fed on a trench-fever patient.

The British Commission also turned its attention to the length of time during which a trench-fever patient is capable of infecting lice—in other words, as to how long the virus is circulating in the blood. It is evident that in a disease such as trench fever, in which some patients show evidence of active infection for only two days and others exhibit symptoms for two years, it would be a tremendous, if not impossible, undertaking to determine when every patient is no longer infectious. Both commissions have shown that the virus is circulating in the blood of practically all patients during the first few weeks. Byam [19] and his co-workers demonstrated that lice may abstract the virus from the blood of patients showing evidence of chronic infection as late as the 300th and the 443d day after the onset of the disease. Lice were also infected by patients during periods of intermission from active symptoms in earlier stages. These subjects usually had relapses later. Two of our patients, on the other hand, failed to infect lice that were allowed to feed upon them about the hundredth day after the onset of fever. It seems that when a patient has recovered completely he is no longer a source of danger. It is difficult, however, to determine when this time has arrived, for many patients after long periods of freedom from symptoms have

late relapses. It seems probable that such carriers of the virus, among infested troops, often served to spread the disease throughout the armies.

Both commissions also showed that the virus is not transmitted to the offspring of infected lice through the eggs. The British demonstrated that pediculus capitus can transmit the infectious agent through the excreta in the same manner as does the pediculus corporis. Bedbugs, on the other hand, did not transmit the disease. Although no experiments are recorded on the transmission of the virus by other blood-sucking insects, it seems that the chief offender in the armies was the body louse.

We are now in a position to inquire into the nature of the infecting agent of trench fever. It is found in three different mediums: (1) Blood of patients; (2) urine of patients; (3) the excrement of lice that have fed upon trench-fever patients. Thus a variety of possibilities present themselves for consideration.

The early demonstration that the blood was infectious led many workers to search microscopically for the offending microörganism with widely divergent results. McNee and his collaborators were unable to find anything in blood films that could be definitely established as a microörganism. They were also unable to infect patients with the Berkefeld filtrate of infectious blood. Our own investigations as to the filterability of the virus in the plasma also yielded negative results. On the other hand, one experiment with the filtrate of crushed, washed erythrocytes, known to be infectious, suggested that the negative results with filtrates of plasma containing virus might have been due to the blocking of the pores of the filter with the large colloid particles of globulin and albumin.

In this experiment the patient presented an atypical picture of trench fever, in that he had such symptoms as pain and tenderness in the usual locations, and an enlarged spleen from the second to the eighth week after inoculation, but no definite fever until the fiftieth day. Then, after a short bout of fever, accompanied by an increase of symptoms, the spleen diminished in size, and all of the symptoms of the preceding six weeks disappeared entirely. No other explanation for the peculiar clinical picture

could be advanced except that a very small amount of the virus had passed through the filter, which had not been clogged with the plasma, because this substance had been removed in the washing of the erythrocytes.

After the demonstration of the infectivity of the urine of patients, and of the excrement of infected lice, it seemed advisable to repeat the filtration experiments with these substances, for in them there was probably the maximum quantity of virus with the minimum of admixed colloids. Two sets of experiments were therefore performed: The dried urine sediment collected from several patients was pooled and divided into two portions. One, without further treatment, was applied to the scarified skin of two volunteers in order to prove that the material under consideration was infectious; the other was suspended in normal saline and passed through an unglazed porcelain filter (Chamberland L), which held back bacillus typhosus. Two volunteers were injected intravenously with this filtrate. The controls, inoculated with the unfiltered sediment, developed mild types of trench fever, after incubation periods of fifteen and sixteen days respectively. One of them suffered relapses; the other did not. The mildness of the symptoms induced in these controls indicates that the virus in this particular set of experiments was either attenuated or present only in minute quantities. One of the volunteers, injected with the urine filtrate, did not develop sufficiently distinct symptoms to warrant a diagnosis of trench fever; the other volunteer, inoculated with the same filtrate, developed trench fever after an incubation period of twenty-one days. In order to confirm the diagnosis, however, lice were allowed to feed upon him from the fourth to the seventeenth days, and with their excrement another volunteer was inoculated by cutaneous scarification. He developed absolutely characteristic trench fever after an incubation period of nine days.

The last series of filtration experiments was carried out with the virus contained in the excrement of lice that had fed upon trench-fever patients. One and one-half grammes of this material was collected and divided into two portions. With one of them four volunteers were inoculated, all of whom developed trench

fever after periods ranging from seven to ten days. The other portion was suspended in normal saline, so that the final strength of the suspension was 2 per cent. It was then passed through a Chamberland filter that held back bacillus typhosus. It is calculated that under the pressure conditions (760 mm. Hg.) this filter would hold back any organism larger than that of pleuropneumonia. Three volunteers were inoculated intravenously with this filtrate. One remained free from symptoms. The second, after a period of five days, developed a low-grade septic type of fever lasting seven or eight weeks, during the latter half of which time the pulse rate was much elevated; the spleen was intermittently palpable from the tenth to the thirty-fourth day; pain and tenderness, except headache, however, were never distinct features. In connection with this case, it may be recalled that Byam has demonstrated by inoculation experiments that a patient may have trench fever with an afebrile course throughout the entire period of observation. No other condition could be found in our patient to explain the peculiar clinical picture. The third of the volunteers, inoculated with filtrate of saline suspension of excrement, after an incubation period of twenty-one days, had an attack of trench fever with two relapses. During the first bout of fever there was an accompanying bronchitis; but nothing except the occurrence of trench fever could explain the relapses with typical enlarged spleen, successive crops of macules, and characteristic pain and tenderness.

It seems definitely established, therefore, that the infectious agent, during at least one stage of its development, can be passed through a porcelain filter if the pores of the filter are not blocked with admixed protein. These experiments have been described in detail, because the negative filtration experiments of other workers have cast a certain amount of doubt upon the validity of our results. The failure of McNee, Brunt and Renshaw is easily explained. The only other details of experiments in reference to the filterability of the virus are a set of five reported by Arkwright.[20] Infected lice excrement was suspended in normal saline and subjected to filtration through either Berkefeld or Chamberland filters at different pressures. In two experiments

in which the pressure was between 300 and 400 mm. of Hg., the injection of the filtrate was followed by entirely negative results; in a third, in which the pressure was between 200 and 300 mm. of Hg., the injection of the filtrate into a susceptible subject was followed in eight days by fever and abdominal pain, the causation of which was in doubt. In these three experiments the filter held back bacillus prodigiosus. In two other trials in which the pressure was between 600 and 740 mm. of Hg. and in which the filter allowed bacillus prodigiosus to pass, the injection of the filtrate was followed in one subject by typical relapsing trench fever, and in a second by no unusual symptoms at all. It is of interest to note that in the last two experiments the filtrate was collected from the same material during two successive periods. The advantage of having several subjects with which to test a given filtrate is well illustrated. A similar demonstration was afforded by our filtration experiments.

In connection with the filterability of the virus of trench fever, it may be recalled that a similar divergence in results has existed in the demonstration of the filterability of several of the filter passing viruses. Many experiments were made before it was established definitely that the virus of small-pox and vaccinia was filterable. Ricketts [21] was unable to filter the microorganism shown by him to be contained in the blood of patients suffering from typhus fever. Both Nicolle [22] and Prowazek,[23] on the other hand, have demonstrated that the typhus fever virus, under proper conditions, will pass through a Berkefeld filter. In order to demonstrate the filterability of many unknown viruses suitable conditions must be fulfilled, and these conditions may differ with different microörganisms. On the other hand, filterability does not mean that the microörganism is necessarily "ultramicroscopic" during all the phases of its development. For some years the virus of yellow fever was thought to be ultramicroscopic because of the ease with which it would pass through an earthenware filter; but Noguchi [24] has lately established the spirochætal nature of the microörganism.

Other biologic characters, moreover, place the etiologic agent of trench fever in close relationship with the group of filter pass-

ing viruses. Mention has already been made of the manner in which the virus in infectious urine resists the concentration of salts resulting from desiccation. Byam and his co-workers have demonstrated that the virus in the excrement of lice retains its activity for at least 120 days, even though it is exposed to the ordinary laboratory temperature and humidity and to sunlight. They [25] have also shown that it is not killed by several weeks' exposure to 50 per cent. glycerin. In their hands it resisted dry heat of 80.5° C. for twenty minutes, but was killed by exposure to 100° dry heat for a similar period. When moist heat was applied, it was killed by twenty minutes' exposure at 60° C. In our experiments the virus in infected louse excrement resisted 60° C. moist heat for one-half hour, but was killed after exposure to 70° C. moist heat for a similar period. The discrepancy can probably be explained by the fact that only one series of tests was carried out by each commission; no doubt heat resistance experiments would more nearly correspond, were several series performed. The important lesson from both experiments is that higher degrees of heat are necessary to disinfect the excreta than are required to free clothing from lice and viable eggs.

The low thermal death point of the virus demonstrates that the other resisting qualities of the microörganism are not due to ordinary bacterial spores. The peculiar behavior of the trench fever virus in the presence of various physical and chemical agents practically rules out the possibility that it belongs to the spirochæta group.

Aside from some unsubstantiated claims that a spirochæta is the etiologic agent in trench fever, the most suggestive finding, from the morphological point of view, is that of the so-called Rickettsia bodies. These bodies were first described by Ricketts [26] in the blood of patients suffering from Rocky Mountain spotted fever and in the bodies of the ticks that transmit this disease. A short time later similar bodies were observed by Ricketts and Wilder [27] in the study of typhus fever. These findings in spotted fever have been amply confirmed by Wolbach.[28] In typhus, in addition, Prowazek,[29] da Rocha-Lima [30] and many other observers have shown that lice which had fed upon patients with this

disease pass large numbers of the bodies in their excreta, and also harbor many of them in epithelial cells of the intestinal mucosa.

Morphologically they are small bodies that vary in size from 0.3 to 0.5 by 1.5 microns. In shape they present various outlines: Cocci, diplococci and short bacilli. In the diplococcoid form the two bodies are often joined by a faintly staining substance, so that dumb-bell or figure 8 forms are seen. Observed under the dark field microscope, these forms have a tumbling motion, but possess no distinct motility of their own. They stain readily in films with either Giemsa or concentrated Gentian violet; they are Gram negative, and not acid-fast. With Giemsa stain they take a red violet color of much the same shade as that of the nucleus of a polymorphonuclear leucocyte. Arkwright [31] states that he can distinguish the Rickettsia in lice that have fed upon trench-fever patients from those that have fed upon typhus-fever patients by the following characteristics: In trench fever the bodies are more purplish and smaller; in typhus they are larger and redder. In blood they are best demonstrated in thick drop preparations from which, after drying, the hæmoglobin has been removed by distilled water or acid alcohol. Because of their small size and small numbers in the circulating blood, it is often necessary to make prolonged examination of blood films in order to demonstrate them. They are much more easily found in the bodies of the insect vectors of these diseases. Attempts to cultivate the pathogenic forms on artificial media have resulted in failures; but both Nöller [32] and Jungmann [33] report that they have succeeded in cultivating on dextrose serum agar the Rickettsia bodies found in sheep ticks. The latter observer has shown that this species, the Rickettsia melophagi, is simply a parasite of the tick and does not produce any disease in the sheep harboring the insects. Films made from the culture of Rickettsia melophagi show all of the forms that are seen in excrement and bodies of lice and in the blood of patients.

Early in their studies various German observers described small microörganisms that resembled the Rickettsia bodies of typhus fever in the blood of patients suffering from trench fever.

This finding, combined with the supposed similarity in the mode of spread of the two diseases led Töpfer,[34] Jungmann and Kuczynski [35] and da Rocha-Lima [36] to search for these bodies in the excrement and bodies of lice that had fed upon patients with Wolhynian fever. Their demonstration of Rickettsia bodies in the intestinal mucosa and excrement of these lice was the chief support for their hypothesis that lice were the insect vectors of this disease. They reported that these bodies could not be found in lice until the lapse of at least five days after the insects had fed upon a patient. This time corresponded so closely with the period between relapses in patients with spiky periodic fever that the German observers felt this fact furnished a further support to the hypothesis of the etiologic relationship of these bodies. Jungmann states that he was able to find them in the blood of patients with the spiky type of relapses only at the time of the relapses; on the other hand, he found them in the blood of patients with continuous or typhoid type of pyrexia at any time during their fever. In spite of the attractiveness of this evidence as to the etiologic rôle of Rickettsia, it does not correspond with the findings of the British Commission as to the infectivity of patients for lice. In the experiments of the last-named observers, lice could be equally well infected by feeding upon patients during the febrile and afebrile periods. Jungmann's observations, therefore, merely indicate a correspondence between the demonstrable presence of Rickettsia bodies in the blood and the occurrence of fever.

Jungmann and Kuczynski [37] claim that they were able to find these bipolar bodies in the blood of mice that had been inoculated with the blood of patients or with the excrement of lice that had fed upon patients. Da Rocha-Lima,[38] on the contrary, was unable to infect mice, but reported that he produced the typical disease in seven out of forty-four guinea pigs inoculated with blood, urine or lice from trench-fever patients. He was, however, unable to pass the infection on to a second generation of the animals. In a series of experiments in which he allowed normal lice to bite seventy trench-fever patients, 73 per cent. of the insects showed Rickettsia bodies; on the other hand, 20 per cent. of the

lice that had fed upon patients who were supposed not to have had trench fever also showed the bodies. He explained these findings on the assumption that normal lice might be infected with a non-pathogenic type of microörganism that he called Rickettsia pediculi. Probably a better explanation is that the patients were suffering from atypical trench fever or that some of them had trench fever complicating the disease for which they were admitted to the hospital. Jungmann,[39] in contradistinction to da Rocha-Lima, states that he has never found Rickettsia bodies in lice that have not fed upon either trench-fever or typhus-fever patients. Both of these observers claim that the interval between an infecting feed and the time that the Rickettsia bodies appear in the insects is about five days for trench fever and nine to twelve days for typhus fever.

The British Commission has confirmed with certain exceptions the observation of the German authors. Arkwright, Bacot and Duncan,[40] who carried out this portion of the work, had the advantage of working with a pedigreed stock of lice, as well as with experimentally produced cases of the disease from which to infect the insects. Finally they were able to compare the appearance of the Rickettsia bodies with the infectivity of the lice for normal subjects. They [41] have lately reported that they were able to find Rickettsia bodies in all of 108 boxes of lice that had fed several times upon sixty-four trench-fever patients. In only one out of many lots of the insects that had fed only on normal persons were forms found that suggest trench-fever Rickettsia bodies. In their experiments a volunteer inoculated with a single louse that contained the Rickettsia contracted trench fever, while another subject inoculated with a single louse from the same box, but free from Rickettsia, remained well. There was also a remarkable correspondence between the appearance of Rickettsia bodies in the excrement of lice after the infecting feed and the virus content of the same excrement when inoculated into susceptible volunteers. The interval between the infecting feed and the appearance of the bodies varied between five and twelve days, with an average of from seven to ten days. This time is longer than that reported by the Germans, but corresponds

closely with the average incubation period in patients inoculated with the excreta of infected lice. Lice that were fed upon patients with experimentally produced trench fever during the first day only did not subsequently show Rickettsia bodies; although lice fed later on the same patients did show them. In this connection it is of interest to note that the only lice that were usually not infectious in our original experiments were those that were fed upon patients during the last two days of the incubation period and during the first two or three days of the fever. Blood from these same patients, however, contained virus, as demonstrated by intravenous inoculation. In all types of experiments, with one exception, therefore, there is a striking parallelism between the infectivity of the insect vectors and the appearance of Rickettsia bodies. This exception was reported by Arkwright and Byam [42] and is as follows: Two lots of lice were allowed to feed upon a trench-fever patient; one lot was kept at a temperature of from 27° to 30° C. and developed Rickettsia bodies; the other lot was kept at 17° C. and did not develop them. The excrement from both lots of lice proved to be infectious by inoculation into normal volunteers.

While it is difficult not to believe that there is a causal relationship between the virus of trench fever and the Rickettsia bodies, it will be difficult to establish definitely such a relationship until it is possible to obtain pure culture of the bodies and with them to reproduce the disease. In this connection it must be recalled that the relation of Rickettsia bodies to other microörganisms has not been established. They may be specific microörganisms; they may be a granular stage through which some other microörganism is passing; or, finally, they may be cell inclusions, the result of the action of some invisible virus on the cell protoplasm and thus resemble the Guarnieri bodies in vaccinia, the Negri bodies of rabies, the molluscum bodies in molluscum contagiosum and the cell inclusions in trachoma.

In our efforts to determine the pathogenesis and histological changes in this disease, we are handicapped by inadequate knowledge as to the nature of the virus and by a total lack of autopsy examinations. The non-fatal character of the disease has made

it impossible to examine thoroughly all of the tissues of the body for the site of attack of the virus. In addition, the failure to reproduce the typical disease in lower animals has forced us to resort entirely to the study of the various clinical manifestations in man in order to arrive at some understanding of the nature of the infection.

In the two other well-known diseases that are associated with the appearance of Rickettsia bodies in the insect vectors of the virus it has been established that the chief structures showing definite histologic changes are the small blood-vessels. Wolbach [43] has shown that the reaction in Rocky Mountain spotted fever is "an endangitis, characterized by endothelial-cell proliferation, local necrosis of endothelium and smooth muscle and thrombosis. Perivascular accumulations of large mononuclear cells are of common occurrence." The lesions are limited practically to the skin and genitalia. Fraenkel [44] has demonstrated that the essential lesion in typhus fever is the same; but in the latter disease the vessels of the viscera are also involved. Schminke [45] has compared the histologic changes in the exanthems of trench fever and of typhus and shown that in the hyperemic and œdematous corium of trench-fever macule there is a perivascular lymphocytic infiltration mixed with some polymorphonuclear leucocytes. The endothelium and vessel-wall necrosis and hyaline thrombosis found in typhus-fever lesions was entirely absent. This probably explains why the trench-fever exanthem is not petechial. In typhus fever the intensely toxic nature of the virus leads to an actual death of the cells and often of the patient; while in trench fever the less toxic virus does not lead to a destruction of either cell or host. A similar action on the body of the insect vector of the two diseases has been found. Both the English and German observers have noted that lice that have bitten trench-fever patients live their normal number of weeks; on the other hand, Jungmann and da Rocha-Lima call attention to the fact that the life of lice is shortened by feeding on typhus-fever subjects.

Clinically the main tissues that seem to be involved in trench fever, aside from the skin, are the hæmatopoietic organs and the nervous system. The polymorphonucleosis during the febrile

paroxysms, followed by an increase in the mononuclear elements of the blood, and the peculiar enlargement of the spleen all indicate that the virus has a marked effect upon the blood-forming and blood-destroying organs. There has been much discussion as to the cause of the peculiar pain and tenderness in patients with this disease. The symptoms are not accompanied by other signs of local inflammation of the periosteum, muscles or tendons, such as swelling, redness or œdema. The description of the pains given by many patients resembles the pains that occur in the early stages of tabes dorsalis. Byam,[46] Carmalt Jones[47] and others have called attention to the peculiar distribution of cutaneous hyperæsthesia in the areas supplied by the eighth cervical, first and seventh dorsal, and all the lumbar segments of the cord, during the active stages of the disease. Sundell[48] has observed that later there is a distinct blunting of the cutaneous sensibility over similar areas. These sensory disturbances, coupled with the increase in tendon, cutaneous and pilomotor reflexes, all point to some abnormal condition of the sensory tracts, probably in the regions of the dorsal roots. The condition of "disordered action of the heart," a late complication in certain patients, can best be explained upon the basis of a disturbance of the autonomic nervous control of the cardiac action. In patients suffering from this peculiar group of symptoms or from neurasthenia following an attack of acute trench fever, there is usually evidence that the disease is still active in a chronic form.

The many forms of fever that have resulted from the artificial inoculation of different individuals with the same strain of virus have demonstrated that the various clinical types of the disease are not due to different varieties of the microörganism, as is the case in malaria. The spiky type of paroxysm, requiring but a single day for its completion, can be best explained on the assumption that the virus requires a certain time for its complete development in the tissues of the patient; when that period is complete the microörganisms, or a toxin that they develop as a result of their activity, flood the patient and give rise to the explosive picture. If, on the other hand, the microörganisms are of different age, either as a result of multiple inoculation, or

because of a mixture of virus of different ages, they will attain their maximum growth in the patient's body at different times, and produce a septicæmic or typhoid type of fever.

Recovery from the disease is evidently due to the development of an immunity on the part of the patient. The time required for the development of this immunity varies within wide limits. No doubt, some individuals possess a complete immunity to the infection. In others there is a partial immunity, so that the introduction of the virus into their bodies results in abortive or larval types of the disease. In the majority of patients complete immunity develops only after repeated flooding of the body with the virus, and on the average requires from three to six weeks for its production. Even then it may be only partial—sufficient to hold in abeyance all symptoms until the patient is subjected to some general depressing influence, when a relapse occurs. Among our volunteers we had a number of examples of such relapses after prolonged periods of absence of fever and symptoms; and lately I have seen in a physician a relapse that occurred twenty-six months after the original attack in Flanders. Such prolonged periods of freedom from symptoms with subsequent relapses remind one of similar conditions in malaria and syphilis.

In still a final group of patients months or years are required for complete immunity to develop. This group comprises from 5 to 10 per cent. of all of the patients afflicted with the disease. In them the manifestations assume a subacute or chronic form; the patients are never entirely free from symptoms; occasional low grade fever is found. The condition is variously described by the terms myalgia, neuralgia, neurasthenia, disordered action of the heart, or trench-fever cachexia. Byam and his associates have shown that at least some of these sufferers are carrying the virus in their blood as late as from three to four hundred days after the onset of fever.

The immunity that develops with recovery is of relatively short duration. The British Commission showed that reinfection was possible on the 132nd and 198th days after the onset; Werner[49] reinfected himself six months after his first attack.

On the other hand, the British found it impossible to reinfect some patients at periods varying from 62 to 182 days after the onset. Irregularity in the duration of immunity seems to be as much a feature of the disease as irregularity in the time of development of immunity and as irregularity in most of the symptoms.

The practical application of all the knowledge that has been gained by much effort is that eradication of the louse is followed by a cessation of the disease. The discussion that has arisen as to whether the chief mode of human infection is through the bite of the insects or results from introduction of louse excrement into excoriated skin is more academic than practical. The method of inoculation by applying louse excrement to scarified skin has resulted in much useful knowledge concerning both human and insect carriers of the disease. It has been the experience of many observers that the wholesale application of measures against louse infestation has been followed by a diminution in the incidence of the disease. This was strikingly brought out in the experience in the Third Army of the American Expeditionary Forces.[50] The experience in the Presbyterian Base Hospital Unit[51] of this city showed that infected and infested clothing and equipment may be handled with impunity, provided the people handling such material are protected against lice. The chance for contracting infection from patients was as great, or greater, after May, 1918, as before, but the simple institution of effective measures against the possibility of becoming infested with lice from the patients resulted in practical freedom from new infections among nurses and orderlies.

In summary: During the recent war a disease, hitherto unrecognized as a clinical entity, was widespread throughout the armies on both the eastern and western fronts. Although the manifold forms of the affection make accurate statistics impossible, it is estimated that between 800,000 and 1,000,000 cases must have occurred. Before the influenza epidemic it was the most frequent single disease in several of the armies. While not fatal, it usually resulted in disability for ten to twelve weeks, and in 10 per cent. of the cases was the cause of invalidism for many

months. In such instances the infection is active in a chronic form. The many clinical forms of the disease are apparently not due to the action of different types of microörganism, but to single or multiple infections with a single type of organism. The intensity and duration of an attack seem to depend upon the relation between the infectivity of the virus and the immunity in the patient.

It has been demonstrated that the disease is not a modified form of enteric or typhus fever, but is due to a specific infectious agent. This etiologic agent behaves in the presence of various physical and chemical environments in a manner similar to that of many of the filter passing microörganisms. Under suitable conditions the virus of trench fever will pass through the pores of a filter that are small enough to hold back ordinary bacteria. The virus is found occasionally in the sputum of patients, often in the urine, and always in the blood at some stage. It is also found in the excrement and bodies of practically all lice that have fed several times upon trench-fever patients, after an interval of from five to ten days following the infecting feed. After a louse has started to excrete active virus, it continues to do so for the remainder of its life. The virus is not transmitted to the larvæ of lice through the eggs. The interval elapsing between the time of the infecting feed and the first excretion of virus by lice closely corresponds with the length of the incubation period in men inoculated with a maximum dose of virus. There is a remarkable correspondence in the infectivity of louse excrement and the time of appearance of Rickettsia bodies; these bodies are also demonstrable, with difficulty, in the blood of patients during the periods of pyrexia. The etiologic rôle of Rickettsia bodies, however, as well as the relation of these bodies to microörganisms in general, remains to be established.

While men may be infected by the simple bites of infected lice, they are more surely infected by applying the excrement of such lice to scarified skin; infected lice, living under normal conditions transmit the disease to the majority of, if not to all, men harboring them. As a direct corollary, the eradication of lice is followed by an eradication of the disease.

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RECENT WORK ON PELLAGRA*

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PELLAGRA was discovered in 1735, nearly two centuries ago, by Gaspal Casal, a physician of Asturia, in Spain, who very early recognized the triad of its symptoms, *viz.,* cutaneous, digestive and nervous. The cutaneous manifestations consist of a bilateral erythema appearing rather suddenly upon the exposed surface of the body and being followed by the peeling off (desquamation) of the affected skin. The digestive symptoms consist of stomatitis, constipation and diarrhœa. The nervous manifestations include changes in reflex irritability and sensation, tremors, psychic abnormalities and sometimes convulsions. The diagnosis is entirely dependent on the skin lesions, in the absence of which it is always doubtful. Unless properly treated, the disease runs a very chronic course and often leads to a fatal outcome.

Time does not permit me to go into detail as to the numerous theories which have been advanced in the course of the last two centuries to explain the origin of pellagra. May it suffice to state that over a hundred years ago Marzari put forth his corn theory, according to which pellagra is due to the consumption of a more or less exclusive diet of corn. This theory was later modified by other Italian students of the disease, who attributed pellagra to the consumption of toxic substances contained in "spoiled" corn, which originate in corn through the growth of certain fungi. This theory held a prominent place in the history of pellagra until very recently. Finally, it was claimed by others that pellagra is caused by a specific organism. None of these theories, however, was supported by convincing evidence.

A very significant feature of pellagra is its limited geographical distribution, as may be seen from the accompanying illustration. It was first discovered in northern Spain. About twenty years later its existence was recognized in northern Italy,

* Delivered January 24, 1920.

then in the southwestern part of France, in the Balkans, especially Roumania, and more recently in lower Egypt, Mexico, the West Indies and the United States, appearing in endemic form in all these countries. A few sporadic cases have been reported from Great Britain, Canada, South Africa and India.

The history of pellagra in this country shows that previous to 1908 cases had been placed on record, but its unquestioned recognition as an endemic disease dates from 1908. The United States Public Health Service early recognized the seriousness of the situation and began an extensive study of the epidemiology of the disease. It was shown that, up to 1912, 30,000 cases with a case fatality rate of 40 per cent. had occurred here (Lavinder, 1913). Clinical studies were also begun at the hospital of the Service in Savannah, Ga.; and Doctors Lavinder and Francis (1917) carried out an extensive investigation on the transmissibility of the disease to monkeys by means of various body fluids and excretions obtained from pellagra patients, which led to negative results. In 1909 the Governor of Illinois appointed a commission to study the disease in that state; and the Thompson-McFadden Commission began its work in South Carolina in 1912. More recently, Jobling and Peterson (1916) studied the epidemiology of the disease in Tennessee.

In October, 1913, I was directed by the Surgeon General to investigate the relation between diet and pellagra. During the first three months my efforts were confined mainly to a thorough review of the literature for the purpose of gathering all the available information regarding the characteristics of the diet used by pellagrins. During a visit to the Service Hospital in Savannah in December, 1913, I was much impressed by the evident beneficial effect of a mixed diet on the course of the disease. After consulting the earlier, as well as the recent, literature on pellagra, I found it contained many very positive statements of physicians with a wide experience, to the effect that a mixed diet, including fresh milk, meat and eggs, was the only efficient method of treatment. Thus Casal, Strambio and others speak of the good results obtained with a mixed diet. Roussel, in his admirable "Traité de la Pellagre," states that the real

GEOGRAPHICAL DISTRIBUTION OF PELLAGRA.

Dark shaded portions indicate endemic foci; light shaded portions sporadic prevalence of Pellegra. Note restricted geographical distribution of the disease.

treatment of pellagra is a milk diet, and supports this statement by the histories of a number of cases which were evidently cured by a liberal diet. Lussana and Frua (1856), on a basis of over 8000 cases treated with a liberal mixed diet, claim that the mortality fell from 24.5 to 4.5 per cent., and that the recovery rate increased from 20 to 75 per cent. as a result of this treatment. *The value of the dietary treatment was, therefore, well established and almost universally accepted, even by adherents of the infectious and "spoiled-corn" theories. This was a most significant fact, which gained in importance when it was brought into relation with the characteristics of the diet consumed by persons prior to their attack of pellagra. The striking features of this diet appeared to be its lack in certain animal foods, such as milk, meat and eggs, the same foods which proved to be so beneficial in the treatment of the disease.* The most valuable information on this point was obtained from the writings of Roussel (1845 and 1866), Lombroso (1892), and others, especially from the detailed dietary studies of Wussow and Grindley (Illinois Pellagra Commission, 1911) in several insane hospitals in Illinois, where in 1909 an epidemic of pellagra had occurred. These authors called attention, first, to the insignificant part played in these dietaries by corn products, and, second, to the vegetable character of the diet, especially its "low content in animal protein." In the conclusions of their report, the Illinois Pellagra Commission discredited any causal relation between corn and pellagra, as the corn products constituted only a moderate proportion of the general diet of those affected by the disease. The Commission, however, regarded the deficiency of the diet in animal proteins as merely a predisposing cause which might so alter the body that the infecting organism had a better chance to grow.

A critical analysis of these two conclusions in the light of all the other available information led me to assume that there was a causal relation between a mainly vegetable diet and pellagra, and that there was sufficient ground to blame the diet *as such* for the causation of the disease. This idea was especially strengthened by the extensive dietary studies which had been carried out by Atwater and Langworthy (Experiment Station Bulletins) in

various sections of the United States, and which plainly revealed the fact that while corn entered into the average American diet there was a great difference in the diet of the poorer people living in the South as compared with that of the people in the North. The former live on a largely vegetable diet, in which cereals and pork fat take a predominant part; the latter consume a mixed diet, including a fair amount of milk, meat and eggs. Pellagra is endemic in the South and occurs only sporadically in the Northern states.

The history of pellagra in France added further support to this hypothesis, and from the accounts of Roussel and LeFer (1907) it became very evident that pellagra disappeared from France simultaneously with improved dietary conditions in the affected regions. Here also the available information pointed to a restricted vegetable diet as the cause of pellagra. With the gradual improvement in the economic conditions and a simultaneous change to a diet containing more animal foods, the disease disappeared. In other words, the history of pellagra in France represents a preventive experiment on a large scale in which diet seemed to play an important rôle.

At the time I formulated my hypothesis (1914), it was difficult to explain satisfactorily the *nature of the defect of the vegetable diet* which could be held responsible for the causation of pellagra, although recent observations on the pathology and physiology of nutrition offered certain definite suggestions. Thus, beriberi and scurvy were considered to be caused by a deficiency in the diet of certain substances of unknown chemical composition called "vitamines." The early stages of the fundamental work of Osborne and Mendel and of McCollum and his associates also began to throw new light on the physiological requirements for proper nutrition. The results obtained by these investigators suggested the possibility that a restricted vegetable diet might be defective on account of: (1) A deficiency or absence of certain vitamines; (2) the presence of some toxic substances; and (3) a deficiency in certain essential amino acids (Voegtlin, 1914).

In order to obtain further support for the hypothesis that a restricted vegetable diet is responsible for pellagra, this hypothesis

was put to an experimental test. Extensive feeding experiments were begun in January, 1914, with various species of laboratory animals which were kept on a restricted diet of cereals, tubers or legumes, foods which had been shown to form the bulk of the diet of pellagrins. It was soon found that the animals could not subsist on these diets and symptoms referable to the digestive and nervous systems were observed. The addition of milk and eggs to this vegetable diet led to proper nutrition and well-being (Voegtlin, 1915). Early in the summer of 1914, the Public Health Service organized a hospital in Spartanburg, S. C., for the purpose of studying the relation of diet and pellagra. It was proposed to study here the following three main subjects in outspoken and uncomplicated cases: First, the comparative value of a mixed diet and a restricted vegetable diet in the treatment; second, the abnormalities of the metabolism, and, third, the therapeutic value of extracts made from foods which were supposedly rich in so-called "vitamines."

METABOLISM IN PELLAGRA

Modern medicine is relying to a constantly increasing extent on the study of the metabolism for the proper diagnosis and treatment of disease. Metabolic studies have also been of great assistance in clearing up the cause of certain diseases of unknown origin. For these reasons an exhaustive study of the metabolism of pellagra is very desirable. The work so far accomplished along this line has led to very interesting observations. It was found that the *utilization of food* (Hunter, Givens and Lewis, 1916) is normal except in cases complicated by an intense diarrhœa. A mild degree of diarrhœa so often found in this disease does not seem to prevent a satisfactory absorption of the digested food. A nitrogen retention may often be obtained even on a mainly vegetable diet, the type consumed by the patients before their attack of pellagra. These findings are in agreement with the fact that pellagra often occurs in persons who, to all outward appearances, are well nourished. Pellagra must, therefore, not be looked upon as a disease of deficient nutrition in the ordinary sense.

The *digestive secretions* show some definite, although not constant deviations from the normal. An abundant salivation is often found in cases with a severe stomatitis. Actual measurements of the rate of flow have shown, however, that most patients exhibit a normal rate of salivary secretion. The specific gravity of the saliva is somewhat higher than in the normal secretion, which accounts also for the increase in the various constituents in the fresh saliva. The diastatic power is unchanged (Sullivan and Jones, 1919). In regard to gastric secretion (Hunter, Givens and Lewis, 1916), it was found that a large number of pellagrins, though not all, suffer from anacidity and lack of pepsin. Free hydrochloric acid may be increased, normal, decreased or absent. Pepsin is absent in cases of anacidity. Children are affected in the same way as adults (Givens, 1918). There seems to be no relation between the severity of the disease and the degree of gastric disturbance. In some cases with anacidity and absence of pepsin, the administration of hydrochloric acid by mouth results in the secretion of pepsin. It is interesting to call attention to several cases with anacidity, which as a result of the dietary treatment had lost all clinical symptoms of the disease, and yet had not shown a return of the gastric secretion to normal, even after several months. This points to a more or less permanent damage to the secretory apparatus, which may possibly find its explanation in a permanent anatomical change either of the nervous inervation of the gastric glands, or the glands themselves. No records are available as to the secretion of trypsin or erypsin, but in view of the fact that even cases with a complete loss of gastric secretion showed a good intestinal digestion, it must be assumed that trypsin and erypsin are present in normal amounts, and may take over the function usually performed by pepsin. Trypsin was found in the stomach contents in cases of anacidity, a fact which is probably due to regurgitation of the duodenal contents as a result of the stomach examination.

An examination of the fæces and the urine indicates that pellagra is associated with an increase of *intestinal putrefaction;* the fæces possessing a foul odor and containing an abnormally high amount of indol and skatol (Myers and Fine, 1913); the

urine showing an increase of indican, ethereal sulphates and hippuric acid. It was shown that certain cases on a vegetable diet excrete indol-acetic or indol-aceturic acid in the urine in the place of indican (Hunter, Givens and Lewis, 1916). This increased intestinal putrefaction may be due, at least in part, to gastric anacidity. Whether it may be the cause of some of the manifestations of the disease or whether it is merely the effect of the disease, cannot be decided. It is highly suggestive, however, that a well-marked indicanuria often shows a decided tendency to decline with the simultaneous improvement in the clinical condition of the patient. In our extensive experience in Spartanburg, we also found that a thorough cleaning out of the intestines in severe cases temporarily led to a marked improvement in the clinical condition of the patients so treated.

The *blood* shows sometimes the changes characteristic of a mild secondary anæmia, but often the blood picture is normal (Hillmann, 1913). It is probable that a large number of the cases showing evidence of anæmia are complicated by hookworm disease or malaria, which are very common in countries where pellagra is endemic. The quantitative determination of the ordinary blood constituents (Lewis, 1920), such as urea, sugar, chlorides, calcium, magnesium, sodium and potassium has shown that these substances are present in normal amounts irrespective of whether the patient is on a mixed or a mainly vegetable diet. The total non-protein nitrogen of the blood is higher on a mixed diet than on a vegetable diet, a fact that probably has no particular pathological significance. Jobling and Maxwell (1917) found normal values for the alkali reserve of the blood from pellagrins on a mixed diet. The viscosity showed a slight variation from normal. To summarize, it is seen that the blood shows no striking abnormalities, a fact which must be given due consideration in any attempt to explain the causation of the disease.

As to the *composition of the urine,* I have previously called attention to the increase in the indican, hippuric acid (Murlin, 1920) and the ethereal sulphates. The creatinine coefficient is low, this being probably due to a lowered metabolism in this disease. The purine metabolism appears to be practically normal.[1]

[1] Unpublished observations by M. H. Givens.

There are certain indications that the excretion of the amino-acid nitrogen is increased in cases with gastric anacidity (Murlin, 1920), an observation which points to an imperfect cleavage of proteins in the absence of gastric digestion. The neutral sulphur fraction of the urine is also increased. In summing up the results of the urinary findings, it is evident that the abnormalities which have been observed so far may be referred to disturbances in the gastro-intestinal tract.

In view of the fact that pellagra sometimes occurs in breast-fed infants, it is of considerable interest to obtain some information as to the chemical composition and *food value of the human milk in this disease.* A chemical analysis of milk secreted by several well-marked cases on a vegetable or mixed diet led to the following conclusions (Voegtlin and Harries, 1920) : The volume may be normal or reduced, depending somewhat on the general nutritional state and food consumption of the patient. Very severe cases often secrete only 100 to 300 c.c. of milk or less per day, whereas we have records of milder cases which yielded approximately one-half to one litre. Lactose, fat, protein-nitrogen and total-solids were found to fall within the normal limits, but considerably below the normal average. The total-ash and phosphate content was normal. A slight reduction of calcium, magnesium and potassium was noted, whereas chlorides and sodium were present in larger amounts. The character of the diet has no influence on the percentage composition of the milk, with the exception that a change from a vegetable diet to a mixed diet is accompanied by a marked increase in total non-protein nitrogen. The conclusion to be drawn from these observations is that well-marked cases of pellagra yield a milk which, as far as its composition with respect to the known milk constituents is concerned, does not show a sufficient deviation from the normal to account for the disease in nursing infants. It is interesting to note that the chemical composition of the milk in beriberi, a disease which is definitely regarded as being due to deficiency of the diet in anti-neuritic vitamine, also reveals no abnormalities in its composition as far as this can be determined by chemical analysis. It remains to be seen whether or not the milk in pellagra ever

differs from the normal with regard to its content in so-called vitamines. This important question can only be settled by the determination of the biological food value of such milk by means of feeding experiments on animals.

In closing this chapter, we feel justified in stating that the metabolism in pellagra shows definite deviations from the normal, which may prove to be of value in the diagnosis and prognosis of the disease. In conjunction with the other data to be presented, they may also assist in clearing up the still somewhat obscure etiology.

INFLUENCE OF DIET ON THE COURSE OF PELLAGRA

I have previously called your attention to the good results obtained in the treatment of pellagra by means of a diet containing a considerable amount of milk, eggs and meat. The question arises, Is the diet the essential factor in this treatment. Without some convincing evidence to the contrary, it might be argued that other factors involved in the hospital treatment, rest and drugs, might account for the improvement in the clinical condition of the patient. This question was put to a test when the Pellagra Hospital in Spartanburg was opened in the summer of 1914. Upon admission to the hospital, the patients with a moderate attack of pellagra and uncomplicated by any other disease were put on a diet which in all essential respects closely resembled the diet which these patients had consumed before being attacked by pellagra. As will be seen from the accompanying table, this diet (A) is mainly composed of vegetable foods, cereals, potatoes and a small amount of green vegetables, also containing a very small quantity of lean meat and milk. It contains a fairly great variety of foods, a relatively low protein and high carbohydrate content, a sufficient fuel value and is representative of the diet consumed by a considerable portion of the population in that section of the country. The patients received the very best medical attention. All drug treatment was omitted. The food was carefully prepared and the actual food consumption determined in the case of each patient during the entire period of confinement to the hospital. A careful,

detailed clinical record was kept. The results of this treatment on over 100 cases may be briefly summarized as follows: Almost without exception the general clinical condition of these patients remained either stationary or gradually became more aggravated simultaneously with an increase in the pellagrous manifestations. The skin lesions often spread to parts of the body which had not been affected previously; there was also an increase in the stomatitis and the gastro-intestinal symptoms. The appetite, as a rule, was good for the first few weeks but diminished gradually. The nervous manifestations, such as disturbances in sensation, reflexes and mentality either showed no change or increased in severity. A few cases developed an acute psychosis. A careful examination of the dietary record showed that the patients had consumed sufficient food. The patients were then changed to a diet (B) which differed from the former in containing one litre of milk, about four eggs and 100 grams of fresh beef. On this diet the patients gradually improved to a surprising extent, the improvement ending in many cases in the complete disappearance of all recognizable manifestations of the disease. Another group of patients was placed upon this same mixed diet immediately after their admission to the hospital, with the result that most cases began to show definite improvement within two weeks, this improvement finally resulting in the course of two months or more in the apparent recovery of the patient. A relatively small number of cases in a far-advanced stage of the disease did not improve, in spite of the same dietary treatment. This is to be expected, however, in such a disease, which is known to lead ultimately to serious anatomical lesions in various organs, especially the central nervous system, the repair of which, if it takes place at all, requires a long period of time. On the whole, these experiences have shown us conclusively that a proper diet, containing a sufficient amount of milk, eggs and meat, is the essential factor in the treatment and determines the course of the disease.

It now becomes a matter of the greatest importance to discover the reason for the therapeutic and presumably the prophylactic value of these animal foods (Voegtlin, Neill and Hunter,

1920). For this purpose, patients with a well-marked attack of pellagra were put on the restricted vegetable diet "A" as soon as admitted to the hospital. The general care of the patients and the control of the diet were the same as in the previous series of cases. Other patients were kept under constant observation in their homes in the neighborhood, the diet and other hygienic conditions remaining the same as they had been previous to the patients being attacked with pellagra. A daily record of the foods consumed by these patients was kept by the patient himself or his relatives, and the general character of the diet was verified as far as possible by frequent visits to the home. During a preliminary period of several weeks the clinical condition of

TABLE

Composition of diet A, complete.

Food.	Amount of food (gms.).	Protein (gms.).	Fat (gms.).	Carbohydrate (gms.).	Calories.	CaO (gms.).	MgO (gms.).	Na_2O (gms.).	K_2O (gms.).	Cl (gms.).	P_2O_5 (gms.).
Wheat bread..	300	25.0	10.2	144.7	790	0.075	0.081	0.120	0.438	0.210	0.600
Butter........	30	.3	24.8	......	232	.006	.001	......	.006	......	.009
Cabbage......	100	.7	.4	3.7	22	.068	.026	.050	.450	.030	.090
Corn meal....	50	4.1	1.8	36.5	183	.007	.065	.015	.085	......	.150
Ham.........	25	6.0	3.7	......	59	.008	.010	......	......	......	......
Hominy......	75	6.0	1.0	54.9	262	.010	.097	.022	.128	......	.225
Corn sirup....	30	......	......	21.3	84	......	......	......	......	......	......
Pork.........	50	1.5	45.3	......	428	......	......	......	......	......	......
Potatoes......	150	2.4	......	21.5	98	.024	.054	.037	.800	.045	.210
Prunes.......	30	.6	.2	20.8	88	.018	.024	.030	.360	.003	.075
Turnip tops...	100	.5	.5	5.7	38	.480	.050	.110	.370	.170	.110
Sugar.........	40	......	......	39.9	158	......	......	......	......	......	......
Milk..........	40	1.4	1.9	1.8	31	.068	.008	.027	.068	.048	.086
Total.....	....	50.5	89.8	350.8	2,473	.764	.416	.713	3.146	.506	2.110

Composition of diet B, complete.

Food.	Amount of food (gms.).	Protein (gms.).	Fat (gms.).	Carbohydrate (gms.).	Calories.	CaO (gms.).	MgO (gms.).	Na_2O (gms.).	K_2O (gms.).	Cl (gms.).	P_2O_5 (gms.).
Wheat bread..	300	25.0	10.2	144.7	790	0.075	0.081	0.120	0.438	0.210	0.600
Butter........	45	.5	37.2	......	348	.009	.001	......	.009	......	.014
Corn meal....	50	4.1	1.8	36.5	183	.007	.065	.015	.085	......	.150
Eggs.........	100	13.4	16.8	......	211	.093	.015	.200	.165	.100	.370
Meat.........	100	21.1	1.3	......	98	.011	.040	.090	.420	.050	.500
Orange juice...	100	......	......	7.9	32	.050	.020	.010	.220	.010	.030
Potatoes......	150	2.4	......	21.5	98	.024	.054	.037	.800	.045	.210
Prunes........	30	.6	.2	20.8	88	.018	.024	.030	.360	.003	.075
Sugar.........	40	......	......	39.9	158	......	......	......	......	......	......
Milk..........	1,000	35.8	47.8	44.9	775	1.680	.190	.680	1.710	1.200	2.150
Total.....	....	102.9	115.3	316.2	2,781	1.967	.490	1.182	4.207	1.618	4.099

the patient was carefully followed. As soon as it was definitely seen that the case remained stationary or was getting progressively worse, a fat-free alcoholic extract, prepared from yeast, rice polishings, ox liver, or thymus gland, was administered daily for several weeks. The preparations made from yeast and rice polishings were chosen for their high content in antineuritic vitamine, as shown by their efficiency in the treatment and prevention of polyneuritis in pigeons. These preparations do not contain the antiscorbutic or fat-soluble vitamine. The reason for the selection of the extracts from liver and thymus was based on the assumption that animal foods, and particularly the liver, in all likelihood would contain at least two different vitamines, *viz.*, the fat-soluble and the antineuritic.[2] For various reasons only thirteen cases yielded results which were above criticism. These are highly suggestive, however, and it is hoped that this important phase of the work will be extended by other investigators. Briefly stated, the results were as follows: First, the administration of yeast and rice extracts over a considerable period of time and in large amounts failed to modify the course of the disease, with the possible exception of one case in which this treatment coincided with the disappearance of well-marked nervous symptoms. This clearly indicates that the defect of the so-called pellagrous diet is not due simply to a deficiency in antineuritic vitamine, as it cannot be corrected by the administration of relatively large amounts of this substance. Second, the administration of the liver preparations to pellagrins was followed by an improvement in their condition, apparently comparable to that produced by the consumption of a diet containing a considerable amount of milk, eggs and meat. The evidence so far available, therefore, indicates that the dietary defect presumably responsible for pellagra is distinctly different from, and probably more complex than, the one causing human beriberi.

THE DIETARY FACTOR IN THE PREVENTION OF PELLAGRA

The correctness of the dietary theory must, at least in part, be based on the prevention of the disease by means of a proper

[2] All details of the preparation, analysis, and biological testing of these extracts will be found in Hygienic Laboratory, Bulletin 116.

diet. Very substantial proof of this sort has been furnished in the case of other diseases of dietary origin. Beriberi, for instance, can be prevented by including in the diet a sufficient amount of foods rich in antineuritic vitamine. Scurvy does not occur if the diet contains fresh vegetables, fresh meat or certain fresh fruits. Xerophthalmia fails to appear if a diet rich in fat-soluble vitamine is consumed. As regards pellagra, I have already referred to the disappearance of this disease from southwestern France, evidently coinciding with a radical change in the diet of the population. It is obvious, however, that in this instance the evidence is by no means above criticism, as the available information in regard to the diet is more of a general nature. Goldberger, Waring and Willets (1915) were the first to show conclusively that pellagra can be prevented by means of an appropriate change in diet. Three southern institutions were selected for the execution of this preventive experiment, two orphanages and a hospital for the insane. In each of these institutions a large number of cases of pellagra had occurred for a number of years previous to the beginning of the preventive test. In the autumn of 1914 the diet in these two orphanages and that in two wards of the hospital for the insane was supplemented by the addition of milk, fresh meat, eggs and dried beans. The general hygienic conditions outside of the diet remained unchanged. In October, 1915, or one year after the change in diet was made, only one out of 244 pellagrins had a recurrence of the disease, whereas on the basis of previous experience there might have been expected approximately 50 per cent. recurrences. Furthermore, there was observed no new case of pellagra among the 168 non-pellagrous residents in the two orphanages. The conclusion to be drawn from this experiment is that pellagra can be prevented by an appropriate diet without any alteration in the other hygienic conditions.

EXPERIMENTAL PRODUCTION OF PELLAGRA

I have now arrived at the crucial phase of the whole pellagra problem, *viz.,* the review of the attempts to reproduce the disease experimentally in the lower animals and in man by means of a

defective diet. The Italian school believed they had produced symptoms resembling pellagra in the lower animals and in man as the result of the administration of extracts of spoiled corn. Raubitschek (1910), on the basis of animal experiments, advanced his very attractive photodynamic theory, which assumes that certain cereals contain a substance which renders the skin oversensitive to sunlight. Critically viewed, none of these experiments stand the test of modern medical science. For this reason I began in January, 1914, an extensive series of feeding experiments on various animals in the hope of being able to produce symptoms and pathological changes resembling those found in pellagra. The results obtained are of sufficient interest to be presented briefly. It was found that a restricted vegetable diet, composed of cereals and tubers and some fresh vegetables, was insufficient to maintain life over a long period of time. The animals developed constipation, followed by diarrhœa, marked changes in reflex excitability, convulsions; a stuporous state was noticed in monkeys. In two of these animals the tongue assumed the characteristic denuded and red appearance seen in pellagra, and the dorsal surface of the feet showed a wet dermatitis. A typical pellagrous dermatitis was never observed in any of these animals. At my suggestion, Doctor Sundwall submitted the tissues of these animals to a careful histological examination, from which he concluded that "there was a striking similarity of cell alterations seen in these animals and in those previously observed in the tissues procured from pellagrins. In fact, practically all the changes noted in the latter were observed in these animals." These changes consist in (*a*) passive congestion in practically all tissues; (*b*) various degrees of retrogressive changes in many of the thoracic and abdominal viscera, such as cloudy swelling, hydropic degeneration, fatty infiltration and degeneration, hyaline and ameloid degeneration; congestion, hemorrhage and ulceration of the gastro-intestinal tract; (*c*) pigmentation, principally hæmosiderosis; (*d*) degeneration in the central nervous system affecting chiefly the reflex arches and the pyramidal nerve tracts (Sundwall, 1917).

Miss Koch and I submitted the various parts of the central

nervous system from some of these animals, and also those from five uncomplicated cases of pellagra, to a detailed chemical analysis. The results showed that both the animal and human tissues differed very markedly in their chemical composition from the normal, and that the changes found in the animal tissues were strikingly similar to those found in the tissues from pellagrins (*Hyg. Lab. Bull.*, 103).

We have, therefore, demonstrated that it is possible to produce in animals, by means of a restricted vegetable diet, both histological and chemical changes, which in all respects, with the exception of the skin lesions, are identical with those found in pellagra. The changes in the spinal cord are of particular significance, as the pellagrous dermatitis has been attributed by pathologists to these central lesions (see Mott, 1913; Singer and Pollock, 1913). The absence of the dermatitis in our animals may possibly be due to essential differences in the reaction of the skin of the various species to such changes. As interesting as these findings may be, it should not be forgotten that these histological changes are not specific of pellagra only.

Another attempt at the experimental production of pellagra was reported by Chittenden and Underhill (1917), who found that dogs, when fed over several weeks or months on a diet composed of "crackers" (made from highly milled wheat flour), boiled peas and vegetable fat, developed symptoms which they considered as resembling those found in pellagra. The animals suffered from diarrhœa, loss of appetite, and developed a marked and extensive ulceration of the oral mucous membrane. The same symptoms were produced in dogs by a diet of white bread, lard and milk. After the addition of fresh meat to the food, the symptoms promptly disappeared. During the last two years I have observed what was evidently the same condition in dogs fed on a diet of white bread and pasteurized milk, the symptoms disappearing after the addition of fresh meat. The ulceration of the oral mucous membrane differs, however, considerably from the pellagrous stomatitis, inasmuch as the marked redness of the tongue and oral mucous membrane so characteristic of pellagra is absent. The skin lesions described by Chittenden and Under-

hill consisted in pustules filled with pus organisms and located on the thorax and upper part of the abdomen. These skin lesions bear no resemblance to those found in pellagra, as they do not show the characteristic distribution and appearance.

I, therefore, believe that we are justified in the conclusion that up to the present time unquestionable pellagra has not been produced in animals, although certain symptoms and pathological changes have been observed in animals on a restricted vegetable diet which greatly resemble the changes found in pellagra.

I shall now refer briefly to an experiment by Goldberger and Wheeler (1915), aiming at the experimental production of pellagra in the human being. Following the classical example of Fraser and Stanton (1909), who produced beriberi in the human by means of a deficient diet, eleven prisoners of a southern prison camp, who volunteered for this experiment, were kept from April, 1915, to October of the same year on a restricted vegetable diet prepared from bolted wheat flour and cornmeal of good quality, polished rice, sugar, pork fat, sweet potatoes and a relatively small quantity of cabbage, collards and turnip greens. At the end of five months six of the volunteers had developed symptoms which were diagnosed as pellagrous. The dermatitis was first noted on the scrotum, later it appeared on the backs of the hands in two cases, and on the neck in one case. Mild nervous and gastro-intestinal symptoms were noted. Although the evidence furnished by this experiment is not very extensive, it appears that pellagra has been produced in the human by means of a restricted vegetable diet.

NATURE OF THE DIETARY DEFECT

I hope you will agree that I have presented a considerable number of facts in support of the hypothesis that pellagra is principally due to the continuous consumption of a restricted vegetable diet. The question arises, Why should a restricted vegetable diet cause pellagra when we know that certain Eastern races live on a vegetable diet without contracting the disease? At the time when I formulated this hypothesis I gathered information which would help to explain this evident discrepancy,

and in the course of the work I have constantly kept this point in mind. What I have to offer are merely suggestions, which may be of value to others in future work.

The available information regarding the composition of the so-called pellagrous diet shows that it is a restricted vegetable diet in which corn, wheat and vegetable or animal ''depot'' fat, play a predominant rôle, with green vegetables forming only a relatively small part of the ration. In the light of the work of Osborne, Mendel and especially McCollum and his associates, it is now evident that such a diet may be deficient in certain essential elements, particularly in protein of adequate composition, vitamines and calcium and sodium. A dietary survey in pellagrous families in South Carolina impressed upon me, furthermore, the fact that both wheat foods and hominy were prepared from highly milled products, which, according to some recent work of Lake, Myers and myself (1918), are more deficient in respect to antineuritic and fat-soluble vitamines and inorganic salts than the whole cereals. I some time ago called attention to the fact that the rapid increase in pellagra in this country during the last twenty years followed soon after the introduction of these highly milled cereal foods (Voegtlin, Sullivan and Myers, 1916). I do not mean to infer that this change alone might explain the increase in pellagra, but I do believe that it represents one of the important factors which, in conjunction with less favorable economic conditions and abnormal dietary habits, has led to the reduction of the food value of the diet consumed by the pellagrous population of the South. The further observation brought out by this dietary survey was the fact that corn bread was often made from cornmeal, baking soda, water and salt, a method of cooking which I was able to show destroys the antineuritic vitamine originally present in the cornmeal. Hence it becomes evident that the use of highly milled cereals and the improper preparation of corn bread still further decreases the food value of the already deficient diet. Is it not reasonable, therefore, to assume that such a diet would lead to a very serious dietary deficiency in both the well-recognized factors as well as the so-called vitamines? For instance, a temporary reduction or elimination of the fresh

vegetables and milk, which are not as easily procurable during the winter months, might lead to the critical reduction in the consumption of the antiscorbutic, antineuritic and fat-soluble vitamine, the calcium, and the protein of proper composition, thus gradually preparing the individual for the attack of pellagra in the following spring and summer months. Such seasonal variations in the incidence of pellagra and in the food supply of the nature just indicated have been noted by those who have paid particular attention to this point. On the other hand, it appears from the dietary studies of Captain McCay (1910) in India and of Yukawa (1909) in Japan that the vegetarians of those countries live on a more nutritious diet, including more green foods, a fact which may explain their immunity from pellagra. This view is supported by the recent observations of McCollum that a properly balanced mixture of seeds and the leafy parts of plants may constitute a satisfactory diet. It is very plain that the restricted vegetable diet which is presumably responsible for pellagra is not properly balanced in this respect.

McCollum, Simmonds and Parsons (1919) have tested the diet used by Goldberger and Wheeler in the production of pellagra on growing rats and have found that young rats are able to live on this diet for at least sixteen months without, however, showing any increase in weight. The animals did not develop any signs of deficiency disease, but looked "very old and rough-haired." On the basis of these and similar experiments, McCollum comes to the conclusion that pellagra is caused by an infectious agent in individuals whose vitality has been lowered by a faulty diet. This conclusion is not necessarily justified. I cannot refrain here from sounding a note of warning against the indiscriminate use of evidence obtained from feeding experiments of one species of animals for the formulation of the dietary requirements of other species. It is to be constantly kept in mind that certain species are more resistant than others to certain dietary deficiencies. Albino rats, for instance, are immune to scurvy, and had it not been that this disease can be produced with the greatest ease in guinea-pigs, by a diet lacking in antiscorbutic vitamine, the dietary theory of scurvy might never have been accepted.

Furthermore, Lake and I (1919) have been able to show that rats are more resistant than cats and dogs to a dietary deficiency of the antineuritic vitamine. Man, on the other hand, is susceptible to all the dietary deficiency diseases which so far have been clearly recognized.

The conception that pellagra is due to a dietary deficiency is, therefore, not contradicted by the available evidence. This does not imply that the disease is necessarily due to a deficiency of the diet in a specific substance, such as the hypothetical pellagra vitamine of Funk (1913). It is more likely that the pellagrous syndrome is caused by a *combination of the deficiencies in some of the well-recognized food factors,* a hypothesis which would account, first, for the resemblance between the symptomatology and histopathology of scurvy, beriberi and pellagra, and, second, for the great individual variation in the symptom complex observed in different patients. Thus, children often exhibit a marked dermatitis without stomatitis or nervous symptoms. The old and much disputed question of ''pellagra sine pellagra'' or, in other words, the occurrence of pellagra without skin symptoms, would also find its solution. Suggestive evidence along this line is found in the favorable results obtained in the treatment of pellagrins with extracts of ox liver, which I previously presented to you. It is very probable that an extension of this work may throw some light upon the nature of the dietary defect. Further attempts should also be made to produce the disease in animals, in view of the fact that the cause of scurvy and beriberi was cleared up largely as a result of the experimental production of these diseases in the lower animals.

SUMMARY

I regret very much that the time at my disposal did not permit me to review critically the evidence which has been put forth in support of the infectious theory. It might appear as if I had purposely disregarded the possibility of pellagra being essentially an infectious disease. May it suffice to state that there is no direct proof that pellagra has ever been transmitted experimentally in man or to animals, although a great deal of effort

has been spent in this direction. The only evidence which at first glance seems to favor the infectious theory is based on epidemiological data.[3] The infectious agent is supposed to be transmitted either by a fly (Simulium) or through human excreta. The proof for these assumptions is indirect in nature and is therefore subject to erroneous interpretation.

The conclusions to be drawn from the recent work on pellagra are the following:

1. The hypothesis that there is a causal relation between pellagra and a restricted vegetable diet has been substantiated by direct proof to this effect and has led to results of considerable practical and scientific value.

2. The metabolism in pellagra shows certain definite changes from the normal, which point to decreased gastric secretion and increased intestinal putrefaction.

3. In the treatment and the prevention of pellagra diet is the essential factor. The disease can be prevented by an appropriate change in diet without changing the other sanitary conditions.

4. A diet of the composition used by pellagrins, prior to their attack by the disease, leads to malnutrition and certain pathological changes in animals resembling those found in pellagra. A typical pellagrous dermatitis has not been observed in animals. Pellagrous symptoms have been produced in man by the continued consumption of a restricted vegetable diet.

5. The nature of the dietary defect has not been discovered, although certain observations point to a combined deficiency in some of the well-recognized dietary factors as the cause of the pellagrous syndrome.

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[3] For information relating to the infectious theory, the reader is referred to an exhaustive article on the subject by Jobling and Peterson (1916—Jr. Inf. Dis. vol. 18, p. 501) and the reports of the Thompson-McFadden Pellagra Commission: Siler, Garrison and MacNeal, 1914, J. Am. Med. Asso., vol. 62, p. 8.

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BLOOD ANALYSIS AND ITS APPLICATIONS *

OTTO FOLIN

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IT is not without misgivings that I have undertaken to lecture before this Society on blood analysis and its applications. To be sure, I have spent many years working in the field of blood analysis, and in the laboratory I could give to an interested clinician instruction in the analysis of blood and urine which, I think, would appeal to him as useful and practical. But analytical problems like those I have been engaged upon during the past eight years cannot very well be made either interesting or instructive from the lecture platform.

The thought will at once occur to you that while the technic itself may be dry and uninteresting the applications of the same to the study of clinical problems must be fundamentally important and of great interest to the majority of medical men who strive to keep up with the advancements in the medical sciences.

Of course, the applications should be interesting. After one has struggled for months and has finally succeeded in finding a convenient, sensitive and accurate method, it is extremely fascinating to apply it to the different kinds of clinical material where one believes or hopes that the new process should reveal some new information. I still remember the pleasure and enthusiasm with which Doctor Denis and myself explored nearly all the hospitals in and around Boston after we had first learned to make quantitative determinations of uric acid in human blood. I can testify to the fact, however, that such occasional surveys of the clinical material available at a particular time seldom yield adequate returns. They consume much time—the hospital supposed to be rich in the material wanted does not have it just then, the clinical histories are not particularly illuminating, the personal impression of the patient fades away, an occasional deter-

* Delivered February 28, 1920.

mination goes wrong and cannot be repeated, except at the cost of another excursion, and if one makes it, the patient has left or is dead. In short, to the laboratory specialist in a medical school the investigation of clinical metabolism problems is not exactly forbidden, but it is beset with so many obstacles not encountered in his other investigations that if his taste is for intensive work he is sooner or later driven to the conclusion that he cannot often afford to leave his laboratory for the sake of hunting clinical material.

In so far as I may refer to "practical applications," therefore, I do so with much diffidence, for it is only at sporadic intervals that I have attempted to make such applications—and that statement applies not only to me but to nearly every worker in the field.

It is not my intention now to dwell upon the somewhat difficult situation confronting biochemists who should be working on clinical material. I refer to it only because it is, in part, though only in part, responsible for the lack of proportion between the search for methods and the applications of methods which has become so conspicuous an aspect of American biochemical research on blood and on urine. I am not prepared to say that this condition has been altogether unfortunate—all who have had occasion to delve into much of the metabolism literature of the past fifty years know what an enormous amount of useless, premature labor has been recorded, the worthlessness of which is primarily due to the use of inadequate analytical methods.

As a perfectly modern illustration of an immoderate amount of so-called practical work and descriptive writings based on blood analysis, one might refer to the recent publications of Johannes Feigl in Hamburg. In the course of the past two years Feigl has published, partly in *Schmiedebergs Archiv.*, partly in the *Biochemische Zeitschrift*, over twenty papers, covering at least seven hundred pages on the chemistry of blood. These writings are, in spots, both interesting and suggestive, and they reveal a perfect familiarity with the literature, including the literature on methods. Yet they furnish very little information not already contained in a few short papers published in the

Journal of Biological Chemistry, papers contributed by half a dozen American investigators.

Feigl is practically the first one in Germany to enter seriously the field of blood chemistry. The subject in its modern development is almost wholly American, although the late Professor Bang in Sweden was intensely active and developed a very comprehensive system of blood analysis which has been used to some extent in Europe. Bang's methods might be called strictly microchemical, for they are based on the use of two or three drops of blood taken from a finger or an ear and collected on a weighed filter paper. The amount of blood taken is thus determined by weight. After appropriate treatment of the paper with various coagulating reagents, the constituent to be determined, such as sugar, non-protein nitrogen, or urea, is extracted and determined by a suitable process devised by Bang. Good work has been done by the help of these methods and on the basis of such tiny quantities of blood. It seems to me extremely unlikely, however, that Bang's methods or any modifications retaining Bang's strictly micro-chemical scale of work will be able to survive in any general sense. The painstaking care required for the weighing of the blood as well as for each subsequent step in the analysis, in order to avoid excessive errors, will inevitably confine their continued use to a few devoted specialists. They are hopelessly unsuitable for regular use in hospitals. But they will not be forgotten. The fact that one can take two or three drops of blood at just as short intervals and just as often as desired will help to preserve those methods for occasional special investigations. Bang's methods were originally published in book form in 1916. They are also described in various papers by Bang in the *Biochemische Zeitschrift,* 1915–18. Bang's technic represents an extreme variation from the processes used in the few blood analyses recorded in the earlier literature when from 20 to 50 c.c. of blood would be used for a single non-protein nitrogen determination.

The blood chemistry developed in this country may, on the whole, be described as a combination of ordinary volumetric procedures with colorimetry and nephelometry. The analytical balance is never used except for the preparation of reagents.

This combination will certainly survive. By using small but readily measurable quantities of blood the preliminary procedures involved in preparing suitable blood extracts are simplified to an extraordinary degree, and possibilities of applying quantitative color reactions to the blood extracts are limited only by the ingenuity of the investigator and the number of blood substances present.

Personally, I feel that we have as yet made only a beginning; we have confined ourselves to the solution of a few obvious problems of more or less direct clinical usefulness or interest. We have remained strictly practical in spite of rather unfavorable conditions, and I think that we must remain so for some years to come. How practical we have been is clearly indicated by the promptness with which busy clinicians adapt all the newer analytical methods to their diagnostic studies of patients. This is good. If only a means could be found for keeping the work of the clinician's "bright girl" out of the literature! I shudder at the thought of the thousands of blood-sugar determinations which have been made in the name of Benedict's method, because so few of them have been made with that combination of checks —of skill, of judgment and alertness—with which Benedict's own sugar determinations are made.

I suppose that the primary reason why I am here to-night to give a lecture on the chemistry of blood is that I published a paper a few months ago which I ventured to call "A System of Blood Analysis." It is always important to find a good title for a paper. My surplus supply of reprints of that one is already exhausted. That paper reflects another aspect of blood analysis as it is being developed in this country. A period of consolidation is well on the way. My so-called system is perhaps the most pretentious illustration, but the tendency to systematize and consolidate blood methods has been strong from the very beginning. Bloor's methods on the blood lipoids represent another compact and time-saving system. Another, covering the inorganic elements, sodium, potassium, phosphates and sulphates will not be long in coming. Preliminary communications pointing in that direction have already begun to appear.

The system devised by myself and Doctor Wu covers the sugar and the water soluble nitrogenous products—the total non-protein nitrogen, urea, uric acid, creatine, creatinine. To all these we are now prepared to add the amino-acid nitrogen (and chlorides). I am sure that it would only bore you to listen to a description of the different individual methods important in our system. We still use the methods exactly as they were described in the original paper, except in one or two particulars. One of these exceptions has to do with the transformation of the urea of the blood into ammonium carbonate preliminary to the removal of its ammonia by distillation. Instead of using a 5 per cent. jack-bean extract in 35 per cent. alcohol, we employ a permanent and very convenient urease preparation in the form of filter paper impregnated with a strong urease solution. This urease paper is made as follows:

Shake 30 grams of jack-bean powder with 10 grams of permutit and 20 c.c. of 16 per cent. alcohol for 10 to 15 minutes. Pour on one or two filters and as soon as the filtration is substantially finished pour the filtrates into a clean flat-bottomed dish. Draw strips of filter paper through the solution and hang them up to dry, just as is done in the preparation of litmus paper. They dry very quickly, and, once dry, the urease seems to keep just as well as it does in the original jack-bean powder. Half a square inch of such paper is enough for each blood urea determination.

The urea determination is important. It is far better to make one non-protein nitrogen determination and one urea determination than to duplicate the former. In connection with the blood urea, I must once more express my opinion of the Ambard coefficient. Neither the original coefficient nor any modification of the same heretofore put forth has any real value. The whole concept really rests on a confusion of two independent processes—the excretion of urea and the excretion of water. The "abnormal" Ambard values encountered in nephritis are far more the result of an abnormal water elimination than of an abnormal excretion of urea. On the other hand, the retention of as little as 3.5 grams of urea nitrogen in a person of average weight (70 K.) will result in an increase, amounting to at least 5

milligrams per 100 c.c. of blood. This simple fact alone furnishes a better starting point for the study of the retention (or elimination) of urea in nephritis in response to a given urea intake than any formula yet concocted on the basis of the Ambard concept.

The consolidation of many different determinations into one system of analysis is extraordinarily advantageous, because it saves so much time and material including the blood. Individual isolated methods will be unable to survive in competition with equivalent methods of such systems. It is, however, more difficult and laborious to work out a really advantageous and sound system than it is to devise the individual methods represented, and if, in the end, the system collapses at some important point the loss is severe and not easily repaired.

Last Christmas, at the annual meeting of the Society of the American Biological Chemists, S. R. Benedict presented a communication on the determination of sugar in blood in the course of which he proved, not only to his own satisfaction, but also, I suspect, to the satisfaction of the majority present, that the blood-sugar method constituting a part of our system of blood analysis is of very doubtful validity—is, in fact, hopelessly unreliable. Benedict's criticisms did not touch our system as a whole—in fact, did not even threaten it, because the essential part of Benedict's own method could be applied to our blood filtrates, as was clearly indicated in an original paper on the subject. But the new blood-sugar determination we considered a very valuable part of our analytical system, especially since Benedict's method has also been more or less under fire.

Our blood-sugar method rests in part on the old familiar reduction process used in every qualitative test for sugar. The new feature is the color reaction by which we subsequently measure the amount of reduced copper. This color reaction is so sensitive that with it one can accurately determine the copper reduced by one-tenth of a milligram of glucose. We certainly could not, therefore, give up this seemingly valuable method without a struggle.

Benedict raised a number of objections, but the essential one

is based on the fact, which we, of course, must admit, namely, that the cuprous oxide produced by the reducing action of the sugar is in part reoxidized to the original shade of cupric copper by the oxygen of the air and so escapes determination. Bang encountered the same difficulty in his work on the blood sugar and solved it by removing the air with carbon dioxide, but in doing so he greatly diminished the practical usefulness of his method. Doctor Wu and I had not made any direct studies of the reoxidation problem, though I personally had earlier paid some attention to it in connection with my method for titrating sugar in urine. I recommended the use of test tubes instead of flasks or beakers for that titration partly because I had found that the reoxidation did not take place to a visible extent in test tubes but did occur when larger vessels are used.

In our blood-sugar work Doctor Wu and I had depended exclusively on indirect check work, and when Doctor Benedict, at the meeting in Cincinnati, informed us that as much as 60 per cent. of the reduced copper might be lost by reoxidation, we had nothing tangible to offer except the general statement that in our hands the final result was reliable—reoxidation or no reoxidation. But that kind of an argument does not carry much weight in scientific circles.

Partly in response to Benedict's criticisms of our sugar method we have worked out a modification published as Supplement I of the "System of Blood Analysis," which is theoretically more correct and which happens to be practically fully as simple and convenient as the original method. With normal bloods the modification and the original method give so nearly the same values that the modification might almost be considered superfluous. This correspondence may not hold for all kinds of blood, however, and where differences do occur the values obtained by the modified methods must be more nearly the correct ones.

In this connection I would call attention to the highly peculiar fact that bloods from nephritics having very high urea retention give by our original method, as by all other sugar methods, abnormally high values for the blood sugar. There does not seem to be any tangible reason why such bloods should contain any

more sugar than does the blood of normal individuals. There is room for the suspicion that in such bloods other materials than sugar play an important part, that similar products in smaller amounts are present in all blood, that all sugar values obtained are high and that the lowest sugar values obtained must still be regarded as maximum values. We know, of course, that creatine and creatinine tend to raise the apparent sugar value of blood in Benedict's method. These products, however, do not have any such effect in our method, yet by our original method we did obtain abnormally high sugar values in bloods containing 150 milligrams or more of non-protein nitrogen per 100 c.c. of blood.

My hope is that our modified sugar method will fail to indicate an increase of the sugar content of such bloods.

There are a number of important problems to be solved on the basis of blood-sugar determinations when once the correct technic has been found. From the nephritic bloods referred to we should get at least some hints as to what other substances besides creatine and creatinine are responsible for the increased reduction.

There is also the important question, much debated, still undecided, as to whether the sugar is all in the plasma, or to what extent the sugar finds its way in and out of the red corpuscles. This is a problem affecting not only the sugar; it concerns all the waste products as well.

A practical problem is that of glycolysis. How is this to be prevented? [This problem has recently been solved—a drop of 40 per cent. formaldehyde added to 5 c.c. of blood will keep the sugar content of the blood constant for almost 48 hours and, strange as it may seem, the formaldehyde does not reduce the copper reagent.] Then there is the old concept of other sugar materials than glucose in blood (Pavy, Lépine). Has this concept any real material fact as background or does it represent only inadequate analytical technic? I am not prepared to express an opinion on this concept, but Pavy's results both for blood and for urine can scarcely be altogether correct.

The next point which I wish to touch upon involves an extension of our system of blood analysis. We have no idea how many non-protein substances are present in the blood filtrate

which constitutes the starting point in our analytical procedures. We know that phenols and other non-nitrogenous products are present, and we know that there are other substances than phenols which behave like phenols with reference to the phenol reagent of Folin and Denis—products which may or may not contain nitrogen. We know that amino-acids are present and that there are other nitrogenous materials, the most important of which, from a quantitative standpoint, are probably more complex than amino-acids—in fact, probably approaching the polypeptides or peptones in the matter of complexity of make-up. Further studies—more extensive subdivisions of the nitrogenous materials in protein free blood filtrates, however obtained—are therefore necessary. By the application of Van Slyke's process it is possible to determine the so-called amino-acid nitrogen, and Van Slyke has done much toward giving us a more satisfactory, because more complete, picture of the distribution of the so-called non-protein nitrogen in blood. Van Slyke's method still requires too much blood, and is too complicated to permit its extensive use in connection with attempts to make complete analyses.

In coöperation with Doctor Wu, I have devised a colorimetric method directly applicable to our tungstic-acid blood filtrates and designed to fill this gap in our system of blood analysis. I cannot go into any detailed description of this new method. It will be published soon in the *Journal of Biological Chemistry*. The problem has been a difficult one, and the method will not be without flaws. There are so many different amino-acids that it would seem *a priori* almost hopeless to try to get a color reaction suitable for such unknown mixtures of amino-acids as are present in blood. It is, however, important to find the best method attainable in this field. Indeed, different methods employing different principles may help much to give us a more comprehensive picture of the composition of the non-protein nitrogen not included in the ordinary nitrogenous waste products. The old peptone problem in connection with blood is gone, but in a new form and in a different connection it is yet destined to be the subject of much investigation. And for such investigations it is essential to be able to determine the amino nitrogen of the

amino-acids. It certainly is far from correct to assume that the undetermined nitrogen (the difference between the total non-protein nitrogen and the nitrogen of the urea, uric acid, creatinine and creatine) represents the amino-acids. For an exaggerated hint of the kind of thing one may expect to find one needs only to apply our analytical technic to the blood of birds. Here the total non-protein nitrogen is high, 45 to 55 milligrams per 100 c.c. of blood, and of that nitrogen less than 10 per cent. is present in the form of urea. Nor is this peculiar proportion to be accounted for on the basis of the uric acid. The uric acid represents only about 5 per cent. of the nitrogen. The amino-acid nitrogen is, to be sure, very high in the blood of birds, but at least 40 to 50 per cent. of the "non-protein nitrogen" in the blood of birds is represented by unknown products. In high nitrogen bloods of nephritics there is little if any increase in the amino-acid nitrogen, but there also one finds an abnormally large unaccounted-for fraction of nitrogen present. A similar condition may be expected, but for a different reason, in the blood of cancer patients. The "undetermined nitrogen" in the urines of such patients is often very large. And it is safe to say that there are other diseases in which human blood will be found abnormally rich in complex nitrogenous products. It is for these reasons, more than for the sake of the free amino-acids by themselves, that the determination of the latter is of importance.

I emphasize these newer aspects of the blood chemistry problem partly to make clear that we are not merely contributing to the problem of nephritis when we investigate nitrogenous constituents of blood. In studying the composition of blood filtrates we are not merely throwing light on the efficiency or the lack of efficiency on the part of the kidneys, highly important as that problem is. In one of our early papers, Doctor Denis and myself ventured to suggest that the problem of deteriorating kidneys must, in part, be solved by prolonged statistical studies. Feigl seems to have made that thought the subject of an exhaustive inquiry, and in one series of four papers he reports 750 complete blood analyses representing the seven ages of man. He confirms our suggestion that with advancing years there may be a gradual

decrease of kidney efficiency without involving clinical nephritis. I regret that his actual figures do not seem to me particularly convincing. Nor am I quite sure that his hurried statistical method is capable of giving a final answer to that problem.

But what we are striving for at present is to reduce the *undetermined* nitrogen in our blood filtrates to the smallest fraction that is practically attainable.

A very important point yet to be solved is the question whether the kidneys are or are not selective with reference to the excretion of the nitrogenous waste products. Are the kidneys of those who have or are going to have gout damaged specifically with reference to their power of eliminating uric acid? That is too fundamental a problem to permit any ill-founded dogmatism. It certainly is true that in those who have gout one is likely to find abnormally high uric acid accompanied by a perfectly normal level for all the other nitrogenous constituents. Whereas in nephritis we may have very high levels of nitrogen retention and substantially normal uric-acid values. I hesitate to say anything very definite on this whole question. Our earlier quantitative uric-acid determinations were subject to considerable errors, and we have to wait for the accumulation of more analytical data of unquestionable reliability.

In connection with the question of the selective activity of the kidneys the ammonia of the blood is interesting. Is the excretory activity of the kidneys more effective with reference to ammonia than to any other products? Neither in nephritis nor in diabetes accompanied by pronounced acidosis do we find more than utterly insignificant traces of ammonia in the blood. The difference between ammonia and uric acid, for example, is certainly remarkable. In the urine these two are very nearly equal in amount, while in the blood there is apt to be at least twenty times as much uric acid as ammonia—in some cases even fifty times as much—and never an abnormally large amount of ammonia. To be sure, one striking and extraordinary exception is said to exist. It has been reported that in epilepsy there is an unmistakable increase in the ammonia of the blood just before the onset of the convulsions. I cannot accept these observations

at their face value, however, until they have received abundant corroboration. Knowing how many times excessively erroneous figures have been reported for this blood constituent, it is well, I think, to be extremely cautious and critical toward all high ammonia results found in human blood. I am sometimes skeptical as to whether there really is any ammonia at all in blood, whether the traces we do find represent anything but postmortem decompositions.

There may be something radically wrong about all methods for the determination of ammonia in blood. Unsuspected chemical combinations may come into play by virtue of which the ammonia is kept in merely potential form and is set free by the kidneys in connection with the secretion of the acid urine. The ease with which ammonia combines with certain aldehydes suggests such a possibility. This problem awaits solution.

In closing, I would again remark that I have only intended to give a fleeting sketch of what we "blood chemists" are trying to do. It is only in the realm of politics that it is proper and laudable to "point with pride" to past achievements. It is less than ten years since this line of work was begun, yet there is scarcely a reputable hospital in America where chemical blood analysis is not now recognized as an indispensable aid in the diagnosis and treatment of patients.

SOME PHASES OF THE PATHOLOGY OF NUTRITION IN INFANCY*

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SINCE the chief function of the infant is growth, it is not surprising that the nutrition of the infant should be the chief concern of those responsible for his welfare. Congenital anomalies of structure, acute and chronic infections, unsuitable food, unhygienic surroundings, too much attention or too little attention; in fact, almost any factor, external or internal, which can affect the infant at all has an influence on his nutrition. Scarcely any one portion or system of the body may become affected without involving the general nutrition. A growing realization that it is the infant as an organic whole that must be considered rather than any individual organ has led to a much broader conception of diseases in infancy and to more rational therapy. This is especially true of those diseases which are associated with gastro-intestinal disturbances. The time has passed when we centre our attention exclusively on the alimentary tract and allow the infant to die of a curable derangement of the intermediary metabolism. The nutrition of the infant now claims our chief attention. The gastro-intestinal tract concerns us for the reason that any alteration in its function exerts a profound influence on the general nutrition.

The great importance of gastro-intestinal diseases as a factor in infant mortality is well recognized. We know that some infants suffering from diarrhœa develop symptoms suggestive of acute poisoning and succumb within a relatively short time, while others lapse into a chronic state of malnutrition, which only too often eventuates in death. We also know that exactly

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the same symptoms may occur in the case of infants who have not suffered from diarrhœa. Czerny recognized this fact and grouped the causes of nutritional disturbances under three main heads: Food, infection and constitution. Granting the importance of these etiological factors, we are still largely in the dark as to how each of them acts, as to what causes the symptoms and even as to why such infants suffering from nutritional disturbances should die. Very little information is obtained from the autopsy room. In the great majority of instances the pathological findings on infants dead of nutritional disturbances are essentially negative.

In the absence of anatomical changes we are forced to conclude that some profound alteration in the chemical or physiological processes in the body must have occurred. This conception has led to much investigation and more speculation as to the nature of these changes, and a popular idea has been that most of the symptoms are referable to toxic substances of metabolic or bacterial origin. Finkelstein and his colleagues [1, 2, 3] have especially emphasized the conception of "food poisoning" as a cause of nutritional disturbances. He considers infection and constitutional abnormalities chiefly as contributory factors in that they lower the infant's tolerance for food, that is, the ability to utilize food without the production of harmful substances. The fact that many of the symptoms are increased when excessive food is given has been the basis for this belief. An entirely different interpretation of this fact may be made, as will be seen later. Finkelstein and his assistants have made numerous attempts to determine the nature of the hypothetical poisons elaborated from food during the processes of metabolism, but the experimental evidence has not been conclusive. Substances capable of producing all of the symptoms have not been found; and no satisfactory explanation has been offered as to the exact mode of action of these hypothetical poisons or of the nature of the peculiar "tolerance" which permits some infants more than others to take large amounts of food without disturbance of the nutrition.

In the absence of proof of a "food poisoning" as the cause

of symptoms, it would seem worth while to search for other possible explanations of the observed facts. It is the purpose of the present paper to present a brief account of such a search.

Two types of nutritional disturbances will be considered, one an acute toxic-like condition usually following severe diarrhœa, the other a chronic state of failing nutrition commonly known as "marasmus." The prominent symptoms of each condition will be mentioned and the cause of these symptoms discussed.

Striking symptoms are usually more easily explained than are less marked ones, so the search for underlying causes began with a consideration of the most stormy of the nutritional disturbances. The condition referred to is known by various names, such as "gastro-intestinal intoxication," "alimentary intoxication" or "toxicosis." The symptoms are, for the most part, hyperacute but occur much more frequently in infants who have for some time been in poor nutritional condition, especially those who have suffered from previous attacks of diarrhœa. Such an infant may develop diarrhœa of more than usual severity. The stools increase in number and lose their normal character, becoming finally little more than brownish water passed in considerable volume, at times almost continuously. The much-used term "cholera infantum" is fairly descriptive of the condition. Vomiting is frequently observed.

Coincident with the development of the diarrhœa, there is a rapid loss of weight which, even in a small infant, may amount to as much as a half pound or a pound in a single day. The whole appearance of the patient changes. The features become sharpened, the eyes sunken and fixed in a far-away stare or turned upwards under the half-closed lids. The skin, especially over the forehead, is likely to assume a slate-gray color. Over the body it hangs in loose folds; it is dry and has lost its elasticity, so that it may be picked up into ridges, which remain an appreciable interval before flattening out. The lips are dry, parched and often of a peculiar cherry-red color. The mouth is held partly open; the tongue is dry. These infants are at first irritable and restless. There is a short, shrill cry frequently repeated. Later the psyche becomes clouded and the infant lapses into a state

of coma. Convulsions not infrequently close the scene. The respirations are deeper than normal, often of the "air-hunger" type, such as is observed in diabetic or uremic coma. The pulse is small, sometimes almost imperceptible, often rapid and irregular. The hands and feet are cold, although the rectal temperature is almost invariably elevated. The urine is very scanty, highly concentrated and may contain traces of albumin and a substance capable of reducing Fehling's solution. The blood is obtained with difficulty. It is thick, does not flow easily and, when centrifuged, separates a relatively small amount of serum. Some degree of leucocytosis is often present. There is in all marked cases a negative nitrogen and salt balance.

This clinical picture is a familiar one; it is described in some detail in order to indicate the nature and scope of the problem of determining the cause of each of the symptoms. The investigations here presented are by no means the first directed towards the solution of the problem. Various explanations for individual symptoms have been offered, but in such a condition as this, when a large number of symptoms are regularly and coincidentally present, one must suspect some underlying cause which provides an adequate explanation for *all* of the symptoms. Obviously the problem would have to be attacked first by a consideration of the individual symptoms.

The particular symptom which has probably received the greatest attention has been the peculiar "air hunger." Czerny [4] first drew attention to this and noted the resemblance of the breathing to that of acid-poisoned animals. He suggested that abnormal acids had entered the circulation. Keller was unable to find such acids in the urine. Steinitz [5] suggested a loss of base from the body in the diarrhœal stools as a cause of the acidosis, but the observations of Holt, Courtney and Fales [6] and of Shohl [7] have failed to substantiate this hypothesis. Doctor Howland and I [8] demonstrated by various tests that acidosis was actually present, often of a severe grade and sufficient in itself to lead to death. We found that acidosis was not the result of overproduction of acetone bodies and suggested that it was, in part, due to a failure of the kidney to excrete acid phosphate. We were

indeed successful in demonstrating an increase in the inorganic phosphate content of the serum and were able to show that a similar phosphate retention occurred in the case of patients suffering from uremic acidosis.[9] We believed the failure of renal function to be a result of excessive water loss from the body by way of the bowel. Oscar Schloss[10] confirmed these findings and brought further evidence of impairment of renal function by demonstrating an excess of urea and total non-protein nitrogen in the blood, reduced phenolsulphonephthalein excretion in the urine and an abnormally high Ambard coefficient. Schloss further demonstrated that the extent of renal function involvement was, in a general way, proportionate to the degree of desiccation of the blood.

That the blood of these infants is concentrated by water loss has been repeatedly shown by various observers (Reiss,[11,12] Salge[13] and Schloss[14]). There is an increase in the specific gravity, in the corpuscular volume and in the amount of dried residue. The index of refraction is increased and the protein content high. The viscosity, the electrical conductivity and the osmotic pressure are all increased. We know from the work of Starling[15] that with a colloidal osmotic pressure of the blood greater than the arterial pressure in the renal glomeruli secretion of urine by the kidney ceases. This is the condition in these infants. They are virtually in a state of uremia as the result of a functional failure of the kidney.

The acidosis explains the air-hunger breathing but not the other symptoms. It is, in itself, not usually the cause of death. It may be overcome by the administration of sodium bicarbonate by mouth or intravenously, but in the great majority of cases symptoms other than those of acidosis are unchanged or may even be increased in severity and the infant succumbs. Treatment which may save the lives of patients suffering from other types of acidosis fails when applied to these infants. It is obvious, therefore, that other and more grave conditions than acidosis must be present and operative.

The clinical picture presented by these infants is in many respects not unlike that of surgical or wound shock. There is

the same gray pallor, prostration, weak, thready pulse and altered character of the respirations and very frequently rapidly fatal termination. The apparent similarity between the two conditions is so close that it has seemed worth while to attempt to determine whether or not some of the same factors were responsible in each.

This is not the place for a detailed discussion of wound shock; suffice it to say there is at one stage a decrease in the amount of blood in currency, due to a passage of plasma through the vessel walls and also to the collection of blood at the periphery, which is thus removed from effective circulation. This decrease in blood volume would lead to an immediate fall in blood pressure were it not for a compensatory constriction of the arterioles. In many instances this compensatory mechanism is inadequate, and a considerable fall in blood pressure occurs. Diminished blood volume further results in a very greatly diminished volume flow of the blood. That is to say, a decreased amount of blood flows through a given portion of the body in a unit of time. Decreased volume flow of the blood leads to an accumulation of acid products of metabolism in the tissues and a decreased alkali reserve of the blood—that is to say, acidosis (Wright and Colebrook,[16] Gesell [17]).

The gray color of the skin, in shock, seems to be due to a stagnation of the corpuscular elements in the capillaries as a result of constriction of the arterioles. Cannon, Fraser and Hooper [18] have shown that red blood-cell counts made on blood obtained from the capillaries by puncture of the skin are very appreciably higher than those made on blood taken directly from the veins.

Thus we see the symptoms of shock largely the result of a suddenly diminished blood volume. What of the infants with diarrhœa who have many of the same symptoms? They, too, have a diminished blood volume. This, as has already been mentioned, is due to a drying out of the blood by excessive water loss.

In order to determine whether or not this decrease in the blood volume results in a diminished volume flow of the blood, we have applied the calorimetric method of G. N. Stewart.[19] The principle of this method is to immerse a portion of an extremity in a measured volume of water at a known temperature, somewhat

below that of the body. The water is contained in a well-insulated calorimeter. At the end of a ten-minute period the temperature of the water in the vessel is measured. The increase in temperature, other factors being equal, is proportionate to the amount of blood passing through the extremity during the period of observation. The volume flow of the blood is conveniently expressed in terms of cubic centimetres per 100 grams of body per minute. Dr. Kirsten Utheim,[20] working in my laboratory, has confirmed the accuracy of the method as applied to small animals by comparison with the results obtained by the use of the ''Strohmuhr,'' measurements being made on the limbs and femoral arteries of dogs.

The Stewart method is easily adaptable to infants by using a ''Thermos'' food jar as a calorimeter. With proper control of the conditions, we found that the volume flow of the blood in the arms or legs of infants could be determined with a very considerable degree of accuracy. It is, of course, essential that the infant should be quiet.

By the use of this calorimetric method, it was found that the volume flow of the blood in the arms of normal infants varied from 15 to 22 c.c. per 100 gms. per minute. Repeated determinations made on the same infant at different times of the day and on successive days gave remarkably constant results. In applying the method to infants suffering from the condition under consideration, a very greatly diminished flow of the blood was found, this being in some instances as low as 2 or 3 c.c. per minute. In the very greatly decreased volume flow of the blood of these infants we have another factor in the causation of acidosis, in addition to the failure of acid excretion already alluded to. From what has been said regarding the nature of the acidosis in these cases, it becomes apparent why the administration of alkali alone usually fails to cure. Sodium bicarbonate administered in isotonic or hypertonic solution does not increase the blood volume or volume flow and does not lower the osmotic concentration of the blood, so that secretion of urine may be resumed. Hypertonic solutions, in fact, have quite the opposite effect.

If the volume flow of the blood through the abdominal vessels

is diminished to any such degree as it is in the extremities, one would expect that the functional ability of the gastro-intestinal tract to care for food would be greatly impaired. Such seems to be the case, for it has been shown by Straub [21] that dogs rendered anhydremic by a diminished intake of water are very prone to the development of diarrhœa and vomiting when fed. The same is certainly true of these infants.

Mention has been made of the presence of a reducing substance in the urine. L. F. Meyer [22] believed this sugar to be lactose or whatever disaccharide was contained in the diet. Finkelstein [23] has explained the appearance of these disaccharides in the urine as the result of a passage of undigested sugar into the circulation through the injured intestinal mucosa. Schloss,[24] on the other hand, found the sugar in the urine to be either glucose alone or glucose in combination with galactose or lactose. A certain amount of lactose can pass through the normal intestinal mucosa, and it may well be the case that when fairly strong solutions of lactose are introduced into the intestinal tract of these infants that some would be absorbed unchanged. As lactose is not altered outside of the intestine, it would be excreted quantitatively in the urine. Even if occurring in the urine, as claimed by Von Reuss and Meyer, the amount is too small to be considered as a factor of any importance in the production of symptoms. The glycosuria, however, requires explanation. It has been shown by Araki [25] that asphyxial conditions occurring as the result of vaso-constriction, hemorrhage or a diminution of the oxygen-carrying capacity of the blood lead to glycosuria. This is generally supposed to be the result of increased glycogenolysis dependent upon acid production in the tissues. In the case of these infants the glycosuria may be readily explained on the same basis.

Diminished blood volume, such as occurs in the condition under discussion, is not necessarily accompanied by a lowering of blood pressure, such as is so frequently observed in shock. We have observed such a lowering only in exceptional instances. The high blood viscosity in these infants is likely a factor in maintaining blood pressure.

It may be well to point out here that, although a diminution in blood volume is common to the two conditions under consideration, the causes for the decreased blood volume are quite different. In the case of infants with diarrhœa, there is a drying out of the blood by water loss; in shock, on the other hand, the diminished blood volume is the result of loss of plasma. The protein concentration of the serum in infants with diarrhœa is high; in shock, normal or low. In this difference we have an explanation of the fact that in some instances the symptoms of the two conditions are identical; in others, quite different.

That the same constriction of the arterioles occurs as a result of the diminished blood volume of these infants, as has been observed in the case of shock patients, would be expected. A comparison of the red blood-cell counts made on venous and on capillary bloods showed a marked concentration of corpuscles in the capillaries. This stagnation of red blood cells in the capillaries as the result of arteriolar constriction may well explain the peculiar gray pallor of the skin, which tends to disappear with establishment of a normal circulation.

From what has been said, it is apparent that the shock-like symptoms of these infants may very reasonably be explained on the basis of the known blood volume decrease.

Constriction of the arterioles leads to a damming back of leucocytes in the capillary blood to even a greater extent than erythrocytes. For example, I have seen a difference of 5000 in the leucocyte counts of venous and capillary bloods from the same infant. A moderate degree of leucocytosis, so often observed in patients of this type, may be, in part, explained by this factor.

Fever, as has been mentioned, is commonly present in infants suffering from severe diarrhœa. Suggested explanations have not been lacking. Finkelstein and his colleagues have considered the fever to be the result of pyrogenic substances in the circulation. The fact that feeding solutions of lactose or of sodium chloride or injecting these substances intravenously, especially to infants already suffering from a nutritional disturbance, results in a rise in temperature has been interpreted as indicating that these substances may exert a direct influence on the nervous mechanism

of the heat centre or may so injure the cells of the body that abnormal metabolic processes are set up, which result in the formation of toxic products capable of causing fever. Both salt and lactose, when injected intravenously, are quantitatively excreted unchanged. It is, therefore, necessary to assume that the effect observed must be of a physical chemical nature and not due to the chemical breakdown of the salt or lactose. These observations of Finkelstein on salt and sugar fever have led to a great deal of controversy. A very good summing up of the literature on this point is found in a recent article by Balcar, Sansum and Woodyatt.[26] Without going into further detail, it may be stated that the weight of evidence seems to support strongly the view that the action of sugar and salt is to remove water from the body, and that the effects observed after the administration of sugar and salt are the result of removal of water from the body. Woodyatt and his collaborators, in the article just cited, bring forward excellent experimental evidence that fever may occur as the result of a decreased amount of water in the body available for evaporation. They have demonstrated that the fever resulting from the administration of solutions of sugar or salts is dependent not upon the total amount of these substances given but upon the amount of water simultaneously introduced into the body. Hypertonic solutions of unutilizable crystalloids leave the body, taking with them water. In the case of the injection of isotonic or hypotonic solutions, or when water is administered simultaneously to supply the water deficit there is, according to these authors, no occurrence of fever.

The infants, of the type which we have been studying, are known to have a diminished water content and a high osmotic pressure of the blood conditions, which, it has been shown, are capable of leading to high temperatures. That these infants show a febrile reaction and that this reaction should be increased by the administration of hypertonic solutions of sugars or salts, as was shown by Finkelstein, is not surprising when we consider the fact that the dehydration is thus increased. There is no need for assuming injury to body cells or the production of pyrogenic metabolites.

Water evaporation is of even greater importance in heat regulation in the infant's body than in that of the adult. Thus Rubner and Huebner [27] have shown that as much as 55 grams of water per kilogram per day may be evaporated from the body of an infant, as compared with a normal evaporation of 22 grams per kilogram per day in the adult. From 30 to 40 per cent. of the total loss of heat from the body is due to water evaporation. The mechanism of water evaporation may well be considered as a safety valve to prevent increase in body temperature. Rubner and Huebner found that when the metabolism of an animal was increased by feeding meat the evaporation of water increased 48.1 per cent., while the total caloric output was increased only 27.7 per cent. When the action of this safety valve is impaired by the increase of osmotic pressure of the body fluids, fever results very much in the same way as the overheating of a gasoline engine when the radiator goes dry. Fever as the result of dehydration has been repeatedly observed in infants, in adults and in animals. Thus L. F. Meyer [28] saw it in the case of infants fed on a concentrated diet, Czerny [29] saw it in cats kept in a warm, dry atmosphere until the blood became desiccated, Jurgensen [30] observed temperatures up to 104° in adults undergoing Schroth's dry diet treatment.

The fever of the infants with the condition described can readily be explained on the basis of the dehydration which is known to be present. The picture is, however, often complicated by other factors. Infection cannot always be excluded. Indeed, in some instances, the presence of a parenteral infection may result in diarrhœa and vomiting, which leads to a dehydration of the body. Under such circumstances the fever may have a double explanation, although Woodyatt suggests that even the fever of infection may be due to an insufficiency of free water in the body.

It has been mentioned that these infants, during the stage of acute symptoms, often excrete more nitrogen and salts than they take in. This negative nitrogen and salt balance can be interpreted only as the result of tissue destruction. That desiccation of the body results in such tissue destruction is well shown by the

experiments of Straub [31] on dogs rendered anhydremic by an insufficient fluid intake. It is further of interest to note that Straub [32] has shown that the administration of salt to such animals results in a still greater negative nitrogen balance. This he interprets as the result of further dehydration brought about by the salt diuresis. Finkelstein has observed the same result following the administration of salt or lactose to infants, but has interpreted it as indicating a toxic action of sugar and salt, a conclusion with no proved basis of fact.

It has been mentioned that infants at about the time of the onset of the severe toxic symptoms suffer a loss in weight, greater than is seen in almost any other clinical condition. Losses of from one to two pounds even in the case of small infants and in a relatively short period of time are observed. This is greater than can be accounted for by anything but water loss. At the same time, examination of the blood shows a concentration which, if indicative of the desiccation of the other fluids of the body, could easily account for all of the loss of weight. The dry skin, lustreless eyes and sunken fontanelle are clinical evidence of this water loss.

The conception presented gives us one explanation for the more frequent occurrence of the toxic states in warm weather. It has been shown [33] that an increase of external temperature from 20° to 36° C. may lead to a 600 per cent. increase in water elimination by the skin and lungs. In the case of infants with a lowered water reserve such excessive loss by evaporation may easily lead to desiccation with its resulting symptoms. Rietschel [34] observed the development of toxic symptoms when weak infants were exposed to high room temperatures, and Finkelstein observed a lessening of intoxication symptoms when the infants were removed to cooler surroundings. In excessively hot weather infants, whether suffering from diarrhœa or not, sometimes lapse into a state indistinguishable from that described as alimentary intoxication. The term "heat stroke" has been applied to this condition. There is little doubt that it is often the result of a desiccation of the body.

The nervous symptoms presented by these infants are a com-

bination of those observed in uremia and in shock. That the infants are virtually suffering from both of these conditions has already been shown.

To sum up: The entire clinical pictures presented by infants who have lapsed into a toxic, shock-like condition following severe diarrhœa may be explained on the basis of the water loss from the body which is known to occur. That factors other than water loss are operative cannot be denied, but it is unnecessary to assume the existence of other factors in order to explain the observed facts. If poisons are accountable for the symptoms, their origin, nature and mode of action has not yet been explained. The supposed toxic action of sugar and salt have been discussed. Efforts to produce the symptoms in animals by feeding or injection of intestinal contents or extracts of intestinal contents of these infants have failed.[35]

Mellanby [36] has suggested β-imidazolethylamine (histamine), a product of bacterial action on histidine, as a cause of toxic symptoms. This substance, when given by mouth to animals, causes diarrhœa and vomiting and when injected intravenously gives rise to shock-like symptoms, but the condition of the blood after such injection is quite different from that observed in these infants. There is no desiccation and the protein content is low or normal. The same may be said of the action of proteoses, which have been suspected of passing unchanged through the gastro-intestinal wall into the circulation.

So far, no mention has been made of the original cause of the diarrhœa. A full discussion of this question would occupy more time than that allotted to this lecture. Suffice it to say that whether the diarrhœa is the result of an excess of fat or carbohydrate in the food, whether it is secondary to parenteral infections or itself of infectious origin, whether due to nervous influences or the injudicious administration of cathartics, the end result is the same. Once anhydremia has occurred, a "vicious circle" is established which still further results in lowering the functional capacity of the gastro-intestinal tract. Huebner,[37] in voicing his skepticism concerning Finkelstein's conception of a food poisoning as the cause of the symptoms, draws attention to

the fact that the clinical picture of Asiatic cholera, a disease entirely unrelated to food disturbances, is identical with that observed in infants supposedly suffering from food intoxication. He suggests that the younger generation of pædiatricians are probably not familiar with Asiatic cholera and, therefore, take no cognizance of this fact in theorizing about the cause of the symptoms.

If a negative water balance occurring as the result of diarrhœa leads to a characteristic symptomatology, the same symptoms should also occur as the result of a negative water balance dependent upon other causes. This we have found to be the case. Doctor Perkins and I made a number of observations on infants who presented symptoms indistinguishable from those following severe diarrhœa. As a criterion of the degree of desiccation of the body fluids we determined the index of refraction of the blood serum. This determination is one which is easily carried out within a few minutes' time and requires only one or two drops of serum. It has the advantage that it may be repeated at frequent intervals. The refractive index varies with the concentration of solids in solution. As the protein has much greater effect on the index than the other solid constituents of the serum, it is possible, as shown by Reiss,[38] to determine quite accurately the protein content of the serum by means of the refractometer. By the use of this method he found the protein content of the serum of normal infants during the first six months of life to average about 6 per cent. Towards the end of the first year it was often as high as 7 per cent. These figures have been confirmed by Salge [39] and by ourselves. The protein content of the serum normally varies somewhat from day to day in the same infant, but the variations are not great. With a drying out of the blood the protein concentration necessarily increases. Such we have invariably found to be the case in the serums of infants suffering from the intoxication-like symptoms following severe diarrhœa. We have observed an increase in the protein content of the serum of as great as 50 per cent. above the normal for the age. Applying the refractometric method, we were able to demonstrate a state of anhydremia in a number of conditions quite unrelated

to diarrhœa. For example, a microcephalic idiot of five months had taken only extremely small amounts of food or water for some days. This infant, on admission to the hospital, presented the typical symptoms of an intoxication with the sole exception of the diarrhœa. The blood protein was 9.35 per cent. Upon the administration of a very considerable amount of saline parenterally the protein content of the blood dropped to 6.6 per cent. At the same time there was a disappearance of practically all of the symptoms of intoxication. This infant took very little of anything by mouth and two days later the blood protein had increased to 8.4 per cent. and toxic symptoms were again present. The administration of food by gavage resulted in vomiting and diarrhœa, symptoms which had not been previously present. The child lost 400 grams in weight during the succeeding twenty-four hours, and the blood protein concentration rose to 9.5 per cent. The symptoms were those of an extreme degree of intoxication. Despite the parenteral administration of large amounts of saline, it was impossible to maintain a normal water content of the body. The protein concentration of the serum never again became lower than 8.2 per cent. and the symptoms remained present until death occurred. In this case the dehydration was originally brought about by an insufficient fluid intake. When food was given, diarrhœa and vomiting occurred, just as in the case of Straub's dehydrated dogs. The vomiting and diarrhœa in turn still further increased the dehydration.

We have observed a marked degree of anhydremia in infants suffering from pneumonia, from otitis media and from pyelitis. Some of these patients were vomiting and had been refusing part of their feedings. The toxic symptoms were especially marked in those patients showing considerable concentration of the blood.

The literature contains many references to the occurrence in newly born infants of transitory fever, sometimes accompanied by toxic symptoms. The observations of Holt [40] and of Crandall [41] on this condition has led to the view that the symptoms, in at least some instances, are the result of an insufficient intake of fluid. Recently much additional evidence in support of this hypothesis has been brought forward notably by E. Muller [42] and

by Rott.[43] The latter in a small series of cases demonstrated an increased desiccation of the body at the height of the fever.

It is thus seen that desiccation of the body occurs in a great variety of conditions and that the symptoms are essentially the same no matter what the original cause. Diarrhœa is by far the most frequent etiological factor, but I do not feel that sufficient evidence has yet been introduced to warrant the assumption implied in the use of the term "alimentary intoxication" or "food poisoning." In the light of our present knowledge, the term "anhydremia" is accurately descriptive of the underlying factor and seems a suitable one to apply to all of these conditions, irrespective of the original cause.

If an infant suffering from diarrhœa is given food, especially an excess of carbohydrate or fat, the diarrhœa becomes worse and consequently the degree of anhydremia tends to become greater. If food is given to an individual who is anhydremic, even though diarrhœa is not present, it is likely to result in diarrhœa, as has been previously mentioned. Furthermore, it has been shown by Straub, in his experiments on dogs, that anhydremic animals die sooner when food is administered than if they are completely starved, the explanation being that the soluble metabolites accumulating in the blood still further increase its osmotic pressure and decrease the available water reserve. We have in these facts adequate explanation of Finkelstein's observations that the giving of food increased the symptoms of his infants suffering from "alimentär intoxication."

If the symptoms of the condition we are discussing are the result of anhydremia, they should disappear when a sufficient amount of fluid has been introduced into the body. In the case of a moderate degree of anhydremia resulting from insufficient fluid intake the symptoms usually disappear rapidly after the administration of fluid by mouth. In the case of post-diarrhœal anhydremia, the results are less striking. In the first place it is usually impossible to administer a sufficient amount of water by mouth. The water deficit of these patients is approximately the same as the amount of weight lost, that is, it may be from 300 to 1500 grams in even young infants. On account of the fact

that vomiting and diarrhœa are still present and that there is an excessive loss of water by evaporation as the result of increased metabolism, chiefly of protein, water loss is so great that it is difficult to give enough water by mouth to keep the infant in water balance, to say nothing of introducing in a short period of time the extra amount required to make up for the deficit. Normal saline may be given subcutaneously and a small amount intravenously, but these methods are only too often insufficient to restore normal conditions in the blood and tissue. By far the most efficient means of introducing water into infants of this type is by way of the peritoneal cavity. This procedure has been used to some extent in English clinics, but its great value seems to have been little appreciated until Howland [44] made extensive use of it in his clinic. Since that time the method has become widely used, and it has been the general experience that the intraperitoneal administration of large amounts of normal saline at frequent intervals is the most efficient therapeutic measure at present at our disposal. Inasmuch as these children have suffered a loss of mineral matter, as well as of water and protein, there would seem to be a theoretical advantage in administering other salts in addition to sodium chloride. Holt, Courtney and Fales,[45] on the basis of their metabolic studies, have recommended such a procedure. In our experience, Ringer's solution is an excellent substitute for normal saline. It is unnecessary to administer alkali to correct the acidosis unless this is of a severe grade, for when sufficient amounts of water are given the acidosis disappears as the conditions which have led to its production are no longer present.

The loss of water from these infants has sometimes been so excessive that recovery is impossible, no matter what means are used. This, it also has been found, is the case in animals rendered anhydremic by various means. This is presumably on account of the destruction of body protein which is known to occur. Lack of fluid intake rarely leads to such a severe degree of anhydremia that recovery is impossible, unless at the same time there is an excessive loss of water from the body. Thus it has been demonstrated that animals subjected to complete food and water starva-

tion may live for considerable periods of time, providing there is no excessive loss of water by way of the gastro-intestinal tract or by evaporation. Sufficient water is produced in the metabolic processes to provide for the water balance. Any increased water loss from such animals results in the development of acute symptoms ending in death.

Mention has already been made of the fact that many of the infants developing toxic symptoms following diarrhœa are, to begin with, in extremely poor nutritional condition. The increased protein destruction during the period of anhydremia still further affects the nutrition, so that, although recovering from the effects of anhydremia, the infants succumb as the result of the other condition.

In order to spare the protein destruction, the administration of carbohydrate is desirable. During the stage of acute symptoms glucose may, to advantage, be given intravenously, but always at such a rate and in such concentration that glycosuria does not occur. As glucose is completely metabolised, the water in which it is dissolved becomes entirely available. Glucose infusions, temporarily at least, increase the blood volume, and this is an advantage. Glucose in isotonic solution has been given intraperitoneally with excellent result, but in a certain number of instances this procedure leads to quite marked abdominal distention.

So much for therapy based on the conception of the pathogenesis of the condition. Curative measures can accomplish something, preventive ones much more. With an understanding of the nature of the disturbance, the problem of prevention is simplified.

Fortunately, relatively few infants suffering from diarrhœa develop the severe toxic symptoms which have been recounted; it is usually those who have suffered from repeated attacks and whose whole nutritional condition is, as a result, far below par. Infants who are already in a condition commonly referred to as marasmus are those likely to succumb finally to the intoxication of anhydremia. It is this chronic condition of malnutrition which will next be discussed.

Anyone who has frequented the wards of an infants' hos-

pital is only too familiar with the picture of these wasted infants. The condition exists in all degrees of severity, and it is often difficult to state just when it begins. An artificially fed infant may begin to vomit occasionally, the stools may vary from the normal, there may be constipation or more frequently repeated attacks of diarrhœa, the weight fluctuates and then usually declines. If the feedings are increased, diarrhœa results; if decreased, loss of weight continues. In other instances an infant may be thriving until some parenteral infection occurs, which becomes chronic—for example, pyelitis or bronchitis. The weight progressively declines. Other infants fed on very dilute milk or insufficient amounts of proprietary foods never do well, and the weight decline begins almost at birth. Ultimately, in each instance, the infant wastes to a skin-covered skeleton. The paper-thin skin has a gray pallor, the hands and feet are cold, the pulse slow, small and weak, and the temperature often below normal, although heat production, as measured in the calorimeter, is markedly higher per kilo of body per day than that of normal infants. The blood is thin, pale and has a low hæmoglobin and red-cell content. The white-blood count is often moderately increased. The urine is essentially normal in amount and in character, except for a somewhat higher ammonia coefficient. From the metabolic standpoint, the most outstanding features of the condition are an inability to utilize food and a negative nitrogen and mineral salt balance. The picture is that of advanced starvation, but often it is a starvation in the midst of plenty.

Various names, other than marasmus, have been applied to the condition. It is known as "infantile atrophy," "dekomposition" or "athrepsia." The latter term, applied by Parrot, is perhaps most accurately descriptive of the condition and therefore the preferable one.

No anatomical basis for the symptoms of this condition has been found and here, as in the case of the intoxication states already discussed, it is necessary to assume an alteration in the chemical and physiological processes of the body. The fact that some of the symptoms of the two conditions are identical and that one often merges into the other would lead one to suspect the

presence of some common underlying factor operative in both. It, therefore, seemed worth while to apply the same methods previously used in the study of anhydremic cases.

Dr. J. F. Perkins and I began the study with the investigation of the protein content of the serum by the refractometric method. Very soon we were struck by the fact that the concentration of the protein in the serum of these infants was usually lower than the average for normal infants of the same age. The fact that there was also a diminution in the red blood cells and hæmoglobin suggested that either the blood was hydremic by dilution with water or else that a destruction of both serum protein and cells had occurred. If the blood were hydremic there should be an increased blood volume, if destruction had occurred, a decreased volume. In order to determine which of these conditions was present, we made use of the vital red method for blood volume estimation.

In studying seven approximately normal infants under one year of age, two of whom were undernourished but gaining well, we found the average blood volume to be 9.1 per cent. of the body weight. The extreme variations were from 8.0 to 10.8 per cent. of body weight. Applying the same method to eleven athreptic infants, the blood volume was found to average 8 per cent. of the body weight, the extreme variations being from 4.8 to 10.4 per cent. The higher values in general were observed in those infants who might be considered as convalescing from the condition.

It is questionable if relationship to body weight is the best method of expressing blood volume when comparisons are to be made of individuals in different nutritional condition. Adipose tissue being relatively non-vascular, a thin individual of the same length and musculature should have a relatively larger blood volume in proportion to body weight than a fat individual. The bodies of the marasmic infants that we studied were obviously almost free from fat. If the absolute blood volume of these had not been changed during the period of wasting the relation of blood volume to body weight should have been distinctly higher than under normal conditions. The very fact that the infants studied had a lower blood volume both absolutely and in relation

to the body weight indicates that a very considerable destruction of the blood must have occurred along with the breakdown of other parts of the body.

As a result of the decrease in blood volume, one would expect that volume flow would also be diminished. This was found to be regularly the case. The volume flow was often less than one-fifth, occasionally less than one-tenth of the normal. During convalescence the volume flow invariably increased.

An additional factor leading to such poor circulation is the condition of the heart muscle. Electrocardiographic tracings made on the infants of this series by Dr. Hugh McCulloch [46] showed occasionally, but by no means regularly, alterations from the normal complexes. The most marked variations were a low amplitude of all waves, and P and T waves being frequently iso-electric, a lengthened P-R interval and broad Q R S complexes. These variations were seen to disappear during convalescence. Whether these functional alterations are to be attributed to organic changes in the heart muscle or merely to an insufficient circulation through the intrinsic cardiac vessels is problematical. The rapid and complete recovery speaks for the latter supposition.

The decreased blood volume of these infants results in constriction of the arterioles, and this leads to a piling up of corpuscles in the capillary blood. A large number of determinations of hæmoglobin and red blood cells on venous and capillary blood from these infants invariably showed this corpuscular concentration in the capillary blood,[47] the increase being not infrequently as great as 20 per cent. over the venous blood. This fact may explain the gray color of the skin.

Arteriolar constriction may be considered a compensatory mechanism to maintain blood pressure at its normal height. In the case of anhydremia we have seen that the constriction is usually sufficient to maintain blood pressure, but here there is the added factor of increased blood viscosity. In the athreptic infants the viscosity of the blood is not increased and consequently the blood pressure sometimes falls below normal limits.

Sufficient has been said to provide the explanation for such symptoms of athrepsia as are identical with those of anhydremia.

In the light of these facts, it is also easy to understand why an infant with a blood volume already diminished by atrophy should, when that volume is still further decreased by even a moderate degree of desiccation, readily develop the severe toxic symptoms characteristic of anhydremia.

In uncomplicated cases of athrepsia there is no increase in the concentration of the body fluids and no bar to the free evaporation of water, fever consequently does not occur. There is no increase in the colloidal osmotic pressure of the blood, hence no diminution in the amount of urine secreted and no accumulation of urinary waste products in the body. Such acidosis as may occur is to be ascribed to causes other than the retention of acid products by the kidney. The acidosis is probably, in part, due to the diminished volume flow of the blood through the tissues and to a lesser extent to production of acetone bodies, the latter the result of partial starvation. Acidosis is, however, by no means a prominent feature of this condition.

We have no direct proof that the volume flow of the blood throughout the body is diminished to the same degree as in the extremities where it has been found possible to measure it. That some decrease of the blood to other parts of the body does occur would seem likely, and it would not be unreasonable to suppose that such a diminution in the blood flow would seriously impair the functional activity of the gastro-intestinal tract and interfere with the whole nutrition of the body. We know that following hemorrhage the nutrition suffers until the blood is restored; the same is apparently true in the case of athreptic infants, but in these infants there is, unfortunately, very little tendency to build up new blood. Transfusions have a temporary value only unless the underlying cause of body destruction is found and remedied.

So far we have discussed the effects of the breakdown of body tissues, and but little has been said as to its cause. We know that simple starvation or a supply of food insufficient to cover the basal energy requirement of the body results in the destruction of the body itself in order to supply the fuel demands. The stored glycogen and fat are burned in preference to protein, but

when the fat and carbohydrate stores are exhausted a general consumption of protoplasm occurs, as is evidenced by a markedly negative nitrogen and mineral salt balance. In a fair proportion of cases of athrepsia insufficient food intake is the obvious cause. Prolonged underfeeding, either with natural or artificial food, leads to the condition, and once it is fully developed the tolerance for food may be so low that it is impossible to give a sufficient amount to cover even the basal energy requirement.

It has been possible to duplicate very exactly the condition of athrepsia in rabbits by prolonged underfeeding.[48] In such animals the blood volume decreased both absolutely and in proportion to the body weight and surface area. The volume flow of the blood decreased much more proportionately than the blood volume. The corpuscular count and volume diminished. When feeding was begun these animals maintained stationary weights for days, even though given unlimited food. The blood volume was almost uniformly regained before any weight increase was observed. Following this restoration of blood volume and volume flow there was a tendency for the weight curve to start upwards. The majority of the rabbits ultimately made a complete recovery, but in a few the normal volume of the blood was not regained, and all of these did badly, the weight curve remained stationary and ultimately fell; all of the animals died. These experiments serve to emphasize the importance of blood volume in relation to nutrition and lead one to suspect that the "period of repair" observed in the case of infants convalescing from athrepsia is a period during which the restoration of blood volume is occurring. Once this has been accomplished improvement is likely to be rapid and steady. If the blood volume is not regained, the prognosis is poor.

An insufficient intake of food by mouth is by no means the only cause of athrepsia. In many instances the food given an infant is sufficient in calories, but is either incompletely digested and absorbed or else it is not completely utilized by the body tissues after absorption.

Practically every infant normal at birth and free from infection will thrive when fed from the beginning on a sufficient

amount of breast milk, but when the same number of calories or even the same proportion of fat, carbohydrate and protein are fed in the form of cow's milk a certain number of infants fail to gain and ultimately lapse into a state of severe malnutrition. There seems to be something about cow's milk which renders it unsuitable for these infants, but there has been little unanimity of opinion as to just why cow's milk is unsuitable. The teleological explanation that cow's milk is made for the calf and not for the baby hardly suffices without further qualification.

At one time it was believed that the protein of cow's milk was the cause of the trouble, but the modern conception, at least of the German school, seems to be that protein, like the king, can do no harm, an idea which has not gone unchallenged. There are chemical differences in the fat of human and of cow's milk sufficient to account for some but not all of the differences in behavior of the two kinds of milk in the infant's body. The carbohydrates of human and of cow's milk differ only in quantity, but cow's milk cannot be made equivalent to breast milk by merely adding the extra 2.5 per cent. of lactose. The mineral salts of human and of cow's milk are quite different in character and amount, and Finkelstein believes this to be an important factor. According to him, the whey salts of cow's milk may injure the intestinal mucosa and interfere with its functional activity, by way of decreasing its normal secretions and also by permitting the passage of harmful substances into the circulation. With an injured mucous membrane abnormal conditions are favorable for abnormal bacterial activity in the intestine. The whey salts of cow's milk are, in addition, supposed to upset the normal mineral equilibrium of the body and lead to a loss of essential ash constituents.

In the attempt to demonstrate the harmfulness of the whey salts of cow's milk, L. F. Meyer [49] performed his well-known "whey exchange" experiments. He mixed the curds of cow's milk with the whey of breast milk and the curds of breast milk with the whey of cow's milk. Each of these mixtures were fed to infants convalescing from nutritional disturbances. On the basis of a very limited number of experiments, Meyer claimed to

have shown that cow's milk curds in breast milk whey was well tolerated, whereas those infants fed on breast milk curds in cow's milk whey showed an increase in all the symptoms of a nutritional disturbance. He concluded from these experiments that cow's milk whey had a distinctly harmful influence. Such a definite, far-reaching conclusion seems unjustified when we consider the differences in the caloric value of the two mixtures prepared by Meyer and also the different relationships between the organic constituents.

Within the past year Lichtenstein and Lindberg [50] have repeated Meyer's experiments on a large number of infants and have been entirely unable to confirm his results or to substantiate his conclusions. They aptly state that the refutation of this theory amounts to "the removal of one of the cornerstones of Finkelstein's teaching structure."

There is a certain amount of very good evidence that bacterial invasion of the upper intestine may occur in the case of infants suffering from nutritional disturbances. This has been demonstrated at autopsy by Moro [51] and others and by Bessau and Bossert [52] on living infants. This bacterial invasion may well be the factor in interfering with normal processes in digestion and absorption and hence with the actual amount of available food entering the circulation and brought to the body cells.

Abnormal bacterial growth in the upper intestine seems to be more frequent in infants fed on cow's milk, but this is evidently not due to any greater bacterial content of the cow's milk as fed. Furthermore, even apart from any bacterial factor, cow's milk often fails to satisfy the nutritional demands of certain infants.

There is one difference between breast milk and cow's milk which, it seems to me, has not been sufficiently emphasized, although it is mentioned in the literature. That is the high "buffer" value of cow's milk, as compared with breast milk. By buffer value we mean a capacity to unite with relatively large amounts of acid or alkali without a great change in chemical reaction. If the same amount of hydrochloric acid is added to equal volumes of human milk and of cow's milk, it is found that the acidity of the human milk expressed in terms of hydrogen ion concentration is far greater.

When milk is taken into the stomach of a normal infant gastric juice is secreted in such amounts that the stomach contents ultimately reach a certain degree of acidity. This acidity, expressed in terms of H-ion concentration, average about 1×10^{-5}, which is the optimum concentration for rennin action, and is sufficient to inhibit markedly bacterial growth (Hahn [53]). The presence of acid on the gastric side of the pylorus initiates a reflex which allows for the passage of food into the duodenum. Here we know, from the work of Bayliss and Starling,[54] the acid acts on some substance in the mucous membrane which results in the production of the hormone "secretin," a substance capable of stimulating pancreatic and biliary secretion. Such is the normal course of events when an infant is fed on breast milk. Suppose, however, cow's milk, instead of breast milk, is fed. If the same amount of gastric juice is secreted, it is entirely insufficient to render the stomach contents acid to anywhere near the same optimum degree. To bring cow's milk to the optimum acidity of 1×10^{-5}, at least three times as much hydrochloric acid is required as in the case of human milk. (This may be readily demonstrated by titrating breast milk and cow's milk with diluted hydrochloric acid, using as an indicator neutral red, which changes color at a hydrogen ion concentration of about 1×10^{-5}.) We must, therefore, assume that the stomach secretes three times as much acid, or else that the optimum acidity is not reached. To secrete this extra amount is very probably beyond the functional capacity of certain infants, yet if this amount is not secreted, bacterial inhibition and rennin action in the stomach occurs to only a slight degree. Without the passage of a sufficiently acid chyme into the duodenum, secretin formation and the hormone stimulation of the pancreatic and biliary secretion would necessarily be greatly diminished. In the light of these conditions, is it any wonder that certan infants fail to thrive on cow's milk which has been insufficiently diluted?

It is interesting to note that those foods which have been found empirically to be the best tolerated by athreptic infants are those which have a low buffer value or in which the buffer is already partly neutralized by acid. Breast milk, well-diluted

cow's milk with added carbohydrate, lactic-acid milk and protein milk are examples.

Some infants waste even when fed on considerable amounts of breast milk and when there are few gastro-intestinal symptoms. For some reason, these infants are unable to make use of food. Congenital cardiac disease or chronic infections may be present, but occasionally no cause can be found, and we are compelled to make use of Czerny's term, "abnormal constitution," to cloak our ignorance.

Athrepsia is essentially a condition of starvation dependent upon any number of causes. But no matter what the cause, the end result is the same, and that result is destruction of body tissue. In athrepsia, as the name implies, we have a clinical picture due to lack of nourishment. The obvious treatment is to supply food in such form as can be utilized by the body. The amount of food required is large for the basal energy requirement is high, and, in addition, much lost tissue must be replaced. Many of these infants fail to gain on less than 150 or 200 calories per kilo per day. The idea fostered by the German school that the condition is a result of food poisoning has no basis of fact and has resulted in much gross underfeeding of infants of this type. There is no good reason to believe that food, once it has passed the gastro-intestinal tract, is capable of harming these infants—diabetes, of course, being excluded. The feeding of an excess of indigestible food sets up an abnormal condition in the gastro-intestinal tract, so that less food is actually absorbed than when smaller amounts of more easily digested food is given.

Athrepic infants need calories; they also need protein, mineral salts and the necessary accessory substances known as vitamines. Excessive amounts of protein are not required, certainly not more than 10 per cent. of the total caloric intake need be in the form of protein.

Fat is valuable chiefly for its vitamine content (fat soluble A). The digestive tract of these infants is, however, incapable of caring for excessive amounts of fat. Carbohydrates spare protein and are the most easily assimilated of all the foods. Carbohydrate must be relied upon to supply the greater part of the

energy requirement of athreptic infants. It has been shown by Helmholz and Sauer [55] that the metabolic tolerance of these infants for sugar is exceedingly high. The problem is to give considerable amounts of carbohydrate without, at the same time, producing gastro-intestinal disturbance. Dextrin, because it is not readily fermented and on account of the fact that it has a high molecular weight and hence in solution exercises a relatively low osmotic pressure, is less likely to cause trouble in the gastro-intestinal tract than are some other sugars. Starch has some of the same characteristics as dextrin, but is not quite so readily digested. The actual percentage of carbohydrate in the food given is relatively unimportant. The percentage of carbohydrate which can be tolerated by the gastro-intestinal tract is dependent upon the form of mixture in which it is fed, as well as upon the type of sugar. Mixtures of lactic acid whole milk containing as much as 10 per cent. of added carbohydrate are often very well tolerated by these athreptic infants.

Carbohydrate can be given in other ways than by mouth; for example, glucose can be administered intravenously or intraperitoneally; we have repeatedly given small infants more than an ounce of glucose a day by the latter method.

Even though a sufficient number of calories and an abundance of protein is supplied to these infants, they cannot build up protoplasm without mineral matter. The milk given may or may not supply the ash requirement. There may, therefore, be a theoretical basis for the administration of an extra amount of mineral matter. The French have, indeed, claimed beneficial results from subcutaneous administration of diluted sea water.

The accessory food factors or vitamines, which are recognized as essential in the nutrition of the infant, are all contained in milk, food which necessarily forms the basis of the diet of these infants. The vitamine content of milk is known to be sufficient for the needs of normal infants, but recently the question has been raised as to whether or not the vitamine content of cow's milk is sufficient for the requirements of certain athreptic infants. Vitamines, especially the water soluble B have been added to the diet and, according to Eddy and Roper [56] and Daniels and Byfield,[57] with excellent effect.

Mention has been made of the fact that the blood volume of athreptic infants decreases along with atrophy of the rest of the body. The blood volume decrease in itself leads to severe symptoms and seriously interferes with the nutritional processes. The blood volume tends to become restored through the period of repair and is generally restored before the restoration of other parts of the body. Anything that would shorten this period of restoration should favorably influence the nutrition. Repeated blood transfusions and the intravenous injection of colloidal solutions, such as gum acacia, result in an increase in blood volume and volume flow, and are therefore theoretically indicated. I have repeatedly seen apparently good results from the use of such measures.

In the condition of athrepsia, as in anhydremia, the therapeutic indications are clear, but only too often difficult or impossible of fulfilment. We have in one a clinical picture due to lack of water, in the other, lack of nourishment; when these two essentials can be supplied and retained, recovery is possible, but only if the conditions have not existed for such a length of time that the body has been irreparably injured.

This discussion has been concerned with a consideration of some of the alterations in the physiological and chemical processes occurring in the infant's body and with the methods of restoration of normal processes. It is interesting to note that those therapeutic procedures, which are theoretically indicated in the light of recent work, are, for the greater part, exactly those procedures which have best stood the test of time and clinical experience.

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